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SOME CLINICAL ASPECTS OF THE NORMAL ELECTROENCEPHALOGRAM IN EPILEPSY*

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WHAT does it mean if the electroencephalogram of an epileptic patient is normal between seizures? On the one hand, the physician may have been led to believe that an abnormal electroencephalogram is highly characteristic of epilepsy. On the other hand, if he regularly refers his epileptic patients for electroencephalographic study, he forms the impression that, for a goodly portion of them, the tracings, at least at the time of examination, which is almost always done between seizures, are described as normal. This may be true even for patients examined when not taking anticonvulsive medicine.

Statistically, a review of the literature shows that the reported incidence of epileptic patients with normal electroencephalograms between seizures ranges from around 2 per cent to around 20 per cent. Historically, the smaller percentages seem to have been reported by the pioneer investigators. Thus Lennox, Gibbs and Gibbs,[1] in 1940, make incidental allusion to a series, perhaps not unselected, of 94 cases, in which the electroencephalograms were normal in only 2.2 per cent, whereas in a later study, published in 1941, Gibbs and Gibbs[2] say that "in our experience less than five per cent of patients clearly diagnosed as epileptic have an initial record which is clearly normal." In 1941 Jasper and Kershman[3] reported a group of "494 patients with symptoms recognized clinically as epileptic," among whom only 26, or about 5 per cent, gave electroencephalograms in which "no obvious abnormality could be seen." In 1943 Solomon et al.[4] reported that, of 121 Navy recruits rejected with the diagnosis of epilepsy, 22 per cent had normal electroencephalograms. In 1944 Echlin[5] observed that the records were normal in 20 per cent of 100 epileptic patients. Hughes,[6] in 1944, reported that "a single electroencephalogram will give positive evidence of epilepsy in about 80 per cent of cases." In the same year Lambros, Case and Walker[7] stated that, without hyperventilation, the records were abnormal in 75 per cent of patients with clinical evidence of epilepsy. Lennox,[8] in 1945, reported that in his series the electroencephalograms were normal in 18 per cent of patients with grand-mal seizures, 15 per cent with psychomotor seizures and 8 per cent with petit-mal seizures. In 1946 Baudoin, Fischgold and Remond[9] reported a 20 per cent incidence of normal records among epileptic patients examined between seizures. In our own series, discussed below, normal electroencephalograms were noted in 21 per cent of the patients examined between seizures.

So high an incidence of normal electroencephalograms among these patients makes obviously urgent an answer to the question asked at the beginning of this paper. The purpose of this communication is to report at least an initial, tentative and partial answer to that question.

This paper is based on the study of 193 patients attending the Epileptic Clinic of the Nerve Out-Patient Department at the Massachusetts General Hospital. Attendance at the clinic is restricted to patients ten to twelve years old or older. These patients were selected from the total attendance in accordance with only two criteria: the clinical diagnosis of epilepsy should be unequivocal; and for each patient at least one record should have been taken in accordance with a well standardized electroencephalographic procedure.

So far as technical details are concerned, electroencephalograms were recorded on a three-channel or six-channel Grass inkwriting oscillograph of the generally familiar type. In each case six or sixteen scalp electrodes were applied, in addition to two mastoid or ear-lobe electrodes; recordings were made from an extensive variety of scalp-to-scalp (so-called "bipolar") as well as of scalp-to-mastoids-or-ear-lobes (so-called "monopolar") linkages; at the end, the patient was hyperventilated for three minutes and observed for one minute after hyperventilation; and the whole recording was run for about thirty minutes. At the time of the test notes were made whether or not the patient was fasting and had been

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off anticonvulsive medication for forty-eight hours. No record was accepted if made more than four hours after the taking of nourishment.

For the classification of a record as normal, it was required that in normal breathing the predominant frequency should not be slower than 8 per second; frequencies and voltages, except of occipital alpha activity, should be symmetrical on the two sides of the head; there should be no unequivocal waves slower in frequency than 5 per second and higher in voltage than the predominant 8-per-second or faster-than-8-per-second activity; there should

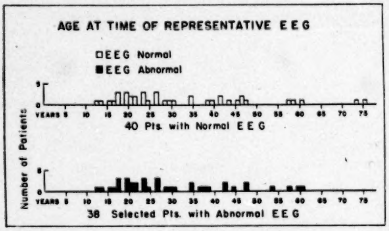
AGE AT TIME OF REPRESENTATIVE E E G
□ E E G Normal
■ E E G Abnormal
Number of Patients
YEARS 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75
40 Pts. with Normal E E G
38 Selected Pts. with Abnormal E E G

FIGURE 1. *Ages of Patients at Time of Normal Representative Electroencephalograms.*

be only rare, single waves down to around 6 per second, and these should not be of higher voltage than the predominant 8 per second or faster than 8 per second; and there should be no paroxysmal runs slower than the predominant 8-per-second or faster-than-8-per-second activity. Regarding overbreathing, especially among subjects ten to twenty years old, a few waves down to 5-per-second frequency were tolerated in the second minute, and a moderately severe but nonparoxysmal break was tolerated in the third minute in records classified as normal.

Among the 193 patients on whom this study is based, there were some from each of whom two or more electroencephalograms were recorded. For each such patient, one record was chosen as representative.

Ages at the times of these 193 tests ranged from ten to seventy-five years, and the largest number of recordings were done on patients who were seventeen years old.

Of these records, 40, or about 21 per cent, were normal, 20, or about 10 per cent, were borderline, and 133, or about 69 per cent, were abnormal.

The upper part of Figure 1 shows the age, at the time of the test, for each of the 40 patients who had a normal representative electroencephalogram.

For a fair comparison of the group of 40 patients giving normal electroencephalograms with the group giving abnormal records, it was desirable that the ages of the patients in the two groups should be the same at the times that the representative electroencephalograms were recorded. A correction for differences of age between the two groups was effected by the selection, from the total group of 133 abnormal records, of a smaller group of 38 abnormal records, in which the average age at the time of the representative electroencephalogram was identical with that in the group of 40 normal records, if from the latter, 2 elderly patients aged seventy-three and seventy-five years at the times of their examinations are excepted. In none of the ensuing comparisons does elimination of these 2 patients alter qualitatively the difference between the two groups. Thus, the lower part of Figure 1 shows, for each of the 38 selected patients with an abnormal representative electroencephalogram, the age at the time of the recording.

At the time of the examination 31, or 77 per cent, of the 40 patients with normal and 30, or 79 per cent, of the 38 patients with abnormal electroencephalograms had received no anticonvulsive medication for at least forty-eight hours.

Figure 2 shows the ages at onset by ten-year periods in the 40 patients with normal and the 38 selected patients with abnormal records. It can be seen that the two groups overlap, the maximum age of onset being in the second, or ten-to-twenty, decade in both groups, but among the patients with normal as compared with those with abnormal records

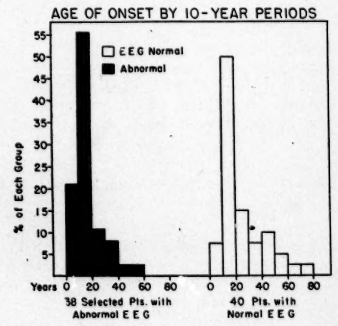
AGE OF ONSET BY 10-YEAR PERIODS
□ E E G Normal
■ Abnormal
% of Each Group
Years 0 20 40 60 80 0 20 40 60 80
38 Selected Pts. with Abnormal E E G
40 Pts. with Normal E E G

FIGURE 2. *Ages of Patients at Onset of Epilepsy.*

the trend was toward a later age of onset: in a number of the latter the chronic adult epilepsy began in the first year of life and continued uninterrupted from then, whereas the earliest age at onset was five years among the former; among the patients with normal electroencephalograms the incidence of onset was higher in the third than in the first decade, whereas among those with abnormal records the reverse was true; and there was a consistently

higher incidence of onset in the fourth and subsequent decades for the patients with normal as compared with those with abnormal records.

In analyzing the types of seizures to which these patients were subject, we made use of an adaption of the seizure classification proposed by Cobb.[10] A graphic summary of this analysis is presented in Figure 3, in which each patient having only one type of seizure is represented by a black entry, whereas each patient having two or more different types of seizures is represented by white entries two or more in number according to the number of the different types of seizures. The columns repre-

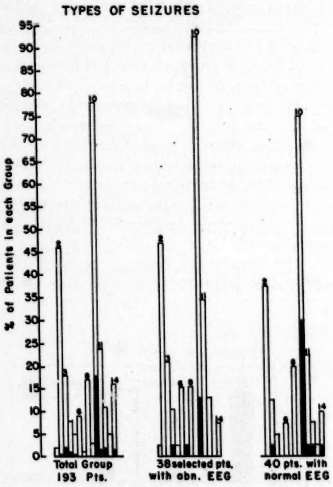

FIGURE 3. *Types of Seizures in Patients with Normal and in Those with Abnormal Electroencephalograms.*

senting the different types of seizures are designated by the numerals "1" through "14," in correct numerical order. Of these numerals, some appear in the graph, and others, omitted through exigencies of space, must be interpolated. The following key correlates these numerals with the types of seizures they represented: 1, giddiness, "faint" feeling; 2, short lapse with or without twitches of face or eyes ("petit mal"); 3, short lapse with muscular spasm or even falling; 4, sudden falling with flaccid muscles (cataplexy); 5, vasovagal and autonomic discharges; 6, sensory fits (identical with aura of motor seizures but without such seizures ensuing); 7, *déjà vue* (dream states); 8, confusion with automatic and locomotor activity ("psychomotor seizures"); 9, ecstasies, rages, furors, fugues ("psychomotor seizures"); 10, clonic or postural convulsions, or both ("grand mal"); 11, clonic or postural convulsions, with asymmetrical features; 12, focal convulsions ("Jacksonian") with or without march; 13, myoclonus; and 14, miscellaneous seizures. Figure 3 shows notably that 40 per cent of patients with

TABLE 1. *Seizures in Patients with Normal and Abnormal Electroencephalograms.*

SEIZURE	PATIENTS WITH NORMAL RECORDS	PATIENTS WITH ABNORMAL RECORDS
	%	%
1 type	40.0	10.5
2 types	27.5	36.8
3 types	27.5	31.6
4 types	2.5	13.2
5 types	2.5	7.9

normal electroencephalograms, as contrasted with only 10 per cent of those with abnormal records, were subject to only one type of seizure. And, in general, the variety of seizures experienced by the former was less than that experienced by the latter. A more detailed analysis of this contrast is given in Table 1.

An analysis of the frequency of seizures for the two groups is presented in Figure 4, which shows that patients with normal records generally had fewer seizures than those with abnormal records. Thus, among the former, the largest number had about three seizures a year, whereas among the latter, the

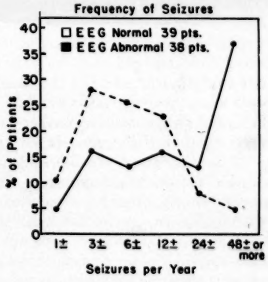

FIGURE 4. *Frequency of Seizures. The dotted line represents patients with normal, and the solid line those with abnormal tracings.*

largest number had about forty-eight or more seizures a year.

Medication, as prescribed at the last visit, was checked for all patients with normal electroencephalograms and for all those of the selected abnormal group. The results of the investigation

are presented in Figure 5, which shows, not for all medication but for all medication common to the two groups, the average dosage in milligrams per day. It will be seen that the daily dosage was very slightly, but still consistently, smaller for all the 40 patients with normal records. Figure 5 also records a gratifying and unexpected result: that 7 of the 40 patients with normal records had discontinued all anticonvulsive medicine by the time

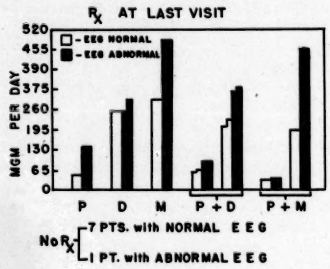

FIGURE 5. *Medication in All Patients with Normal Electroencephalogram and in Selected Patients with Abnormal Tracings.*

The columns with notched tops represent patients given alternative dosages of medicine (such as one or two tablets of mebaral), the lower level of the notch representing the smallest and the higher level the largest average dosage determined by such alternatives. The various types of anticonvulsants prescribed are indicated as follows: P = *phenobarbital;* D = *diphenylhydantoin sodium (dilantin); and* M = *mebaral.*

of the last visit, whereas this was true for only 1 of the 38 selected abnormal group.

A detailed analysis was made of the case data on the 8 patients who, up to the last visit, had successfully discontinued anticonvulsive medication. This analysis suggests that the prognosis for remission of seizures off medicine is favorable under the following conditions: if the patient has had no attacks in infancy; if he shows, other than seizures, no evidence of encephalopathy; if he has been so mildly disturbed and is so well endowed as to have maintained a good social adjustment despite the seizures; if he presents, at the time that withdrawal of medicine is considered, a normal electroencephalogram (perhaps preferably done while the patient is off anticonvulsants for at least forty-eight hours); and if he has been seizure free for a period of one to two years, with anticonvulsants gradually reduced to, and maintained at, a minimal dosage of 1 capsule or tablet of phenobarbital, mebaral or dilantin daily or every other day for three months. The bias of this paper leads to a special emphasis on the normal record as a favorable criterion. A negative family history for epilepsy may also be prognostically favorable. Probably, too, a relatively low maximal incidence of seizures — perhaps less than about twelve seizures a year at the worst period — is favorable. Apparently little prognostic significance attaches to the age at onset for the chronic adult epilepsy, as distinguished from attacks in infancy, the type of seizure or the relative incidence of seizures while the patient is awake and asleep. Finally, it may be added that remission of seizures off medicine is common in the late teens and early twenties.

Regarding the number of seizures while the patient is awake as compared with the number while he is asleep, whether at night in bed or during a daytime nap, one gets the clinical impression that the proportion of seizures while the patient is asleep is higher among patients with normal than among those with abnormal electroencephalograms. This impression appears to be confirmed by the analysis shown in Figure 6. In each group the clinical histories on 45 per cent of the patients failed to indicate any seizures in sleep. For the remaining 55 per cent in each of the two groups, Figure 6 shows a favorable trend toward a relatively higher incidence of seizures in sleep among patients having normal as compared with those having abnormal records.

These patients were also studied for four other features, which are described without graphic representation.

Thus, there was little contrast between the two groups regarding the occurrence of convulsions in

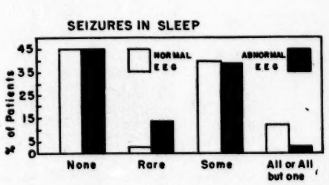

FIGURE 6. *Occurrence of Seizures during Sleep.*

infancy — convulsions, that is, in the first five years of life and separated from the chronic adult epilepsy by a long, seizure-free period. Among the patients with normal records there were 4, or 10 per cent, and among the selected abnormal group, there were 5, or 13 per cent, who gave a history of such infantile convulsions.

There was also little contrast between the two groups in the occurrence of post-traumatic or other encephalopathies, as distinguished from mere electrocortical abnormality. By implication or direct evidence, such encephalopathies were present in 13, or 33 per cent, of the 40 patients with normal and in 14, or 37 per cent of the 38 selected patients with abnormal electroencephalograms.

Seven patients, or 18 per cent, with normal and 10, or 26 per cent, with abnormal records gave a positive family history of epilepsy.

In the three preceding comparisons, the differences were slight, but it may be significant that they were all in favor of the group with normal electroencephalograms.

Among the differences not represented graphically, however, a striking contrast between the two groups of patients appeared in the scholastic and occupational histories. Among those with normal records only 4, or 10 per cent, had been put out of school or had lost or changed jobs, or were unemployed because of their epilepsy; whereas 11, or 28 per cent, among the selected abnormal group had been put out of school or had lost jobs or were chronically unemployed or unemployable.

Discussion

From the observations cited above, it seems reasonable to conclude that a normal or almost normal electroencephalogram should be prognostically favorable and so of practical value, especially if it is recorded at the time of the first seizures when the future course of the illness is still unpredictable, whereas a grossly abnormal record should serve usefully to forewarn the physician of future difficulties and disappointments or to explain such difficulties and disappointments if they are already established.

Summary

Epileptic patients each showing at least one normal electroencephalogram between seizures and those showing only abnormal electroencephalograms between seizures are compared with reference to ten other aspects of the disease. All ten comparisons are favorable to the patients with normal records. In the patients with normal electroencephalograms there were later onset, fewer different kinds of spells, less frequent spells, greater response to medicine, more remissions while off medicine, more spells during sleep and greater ability to work, whereas patients with abnormal records had had spells in infancy, head injuries or other encephalopathies and positive family history of epilepsy.

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SPONTANEOUS PNEUMOTHORAX*

A Clinical Study of One Hundred Consecutive Cases

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IT IS the purpose of this paper to present 100 consecutive, unselected cases of spontaneous pneumothorax in patients admitted to the Boston City Hospital in a nine-year period between 1934 and 1943. During the same period approximately 375,000 patients were admitted to the hospital, giving an incidence of 0.027 per cent, a figure that coincides with that of the series of Cohen and Kinsman.[1]

Diagnosis

The diagnosis in each case was made on the basis of the history, physical signs and x-ray findings. Positive x-ray findings were considered essential, and the diagnosis was not made in their absence.

The patients were divided into two groups, one consisting of 64 cases in which underlying pulmonary disease was known prior to entry or discovered during hospitalization, and the other comprising 36 cases of spontaneous pneumothorax occurring in apparently healthy persons. The older literature attributed a much higher percentage of spontaneous pneumothorax to underlying pulmonary lesions, especially tuberculosis. Of 918 cases collected by Biach,[2] 77.8 per cent were said to be due to tuberculosis. Morse[3] attributed 70 per cent of his 51 cases to tuberculosis, and Ayer[4] 69 per cent of his 72 cases, and West[5] found 99 of his 101 reported cases due to tuberculosis. However, the last series was derived from patients hospitalized for chronic lung diseases. As recently as 1931, Palmer and Taft[6] could find only 70 reported cases of spontaneous pneumothorax occurring in apparently healthy persons. Kjaergaard[7] focused attention on this condition with his monumental series in 1932.

Clinical Picture

The history, symptoms and signs presented by the patients of both groups were essentially the same.

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Twenty per cent of both groups gave a history of unusual exertion prior to the acute episode. Of these, 6 gave a history of strenuous lifting, 4 of severe fits of coughing, 3 of running upstairs, 2 of attacks of sneezing, and 1 each of wrestling, playing tennis, rowing a boat, missing a step going downstairs and cranking an automobile. In the remaining 80 per cent the pneumothorax occurred during usual daily activities or at rest. In their series of 58 cases Ornstein and Lercher[8] found a history of exertion in 22 per cent.

Chest pain occurred in every patient and was always localized to the involved lung, with occasional radiation to the abdomen, neck or lower back. Dyspnea was also universally complained of, but frequently appeared to be more subjective than objective. Cough and fever were common in patients of the first group, but only 5 patients in the second complained of cough, and only 3 had an elevated temperature, which was slight. Hemoptysis occurred in 2 patients with underlying tuberculosis.

The physical signs varied with the degree of lung collapse. It was generally found that when the degree of pneumothorax was more than 40 per cent, classic signs could be elicited. These included hyperresonance, diminished or absent vocal and tactile fremitus, absent breath sounds, mediastinal shift and positive coin test. The physical signs may be scant or absent in the presence of small pneumothoraces. In the first group the additional findings of the underlying pulmonary lesion were also present. Right-sided and left-sided pneumothorax occurred with equal frequency in both groups. One patient with bilateral spontaneous pneumothorax had far advanced bilateral tuberculosis.

Associated Pulmonary Disease

Table 1 shows the incidence of the various pulmonary disorders that were found associated with the patients in the first group. Tuberculosis constituted the underlying cause in 50 per cent of this group and in 38 per cent of the total. As might have been expected, there was a preponderance of cases in males except in the acute disorders, in which the ratio of males to females was about 1:1. The patients in this group ranged in age from twelve to eighty-two years, with an average age of forty-six years and one month. This is in marked contrast to the patients in the second group, who had an average age of twenty-seven years and one month, with a range of three to fifty-three years.

The occurrence of a spontaneous pneumothorax in a patient above the age of forty-five should make one strongly suspicious of the presence of underlying pulmonary disease. The following case illustrates this point.

Table 1. *Incidence of Underlying Pulmonary Disorders in 64 Patients with Spontaneous Pneumothorax.*

Disease	Total No. of Patients	Male Patients		Female Patients		Average Age
		No.	Percentage	No.	Percentage	yr.
Tuberculosis	38	29	76	9	24	44.0
Emphysema	5	4	80	1	20	59.6
Bronchiectasis	5	4	80	1	20	43.0
Postpneumonic empyema	4	3	75	1	25	50.0
Bronchial asthma	3	3	100	0	0	36.0
Lung abscess	3	0	0	3	100	32.0
Metastatic carcinoma of lung	2	2	100	0	0	54.0
Pneumonia	2	1	50	1	50	80.0
Bronchogenic carcinoma	1	1	100	0	0	61.0
Pulmonary infarct	1	0	0	1	100	17.0
Totals	64	47		17		
Averages			73.4		26.6	46.1

K. H. (B.C.H. 1129821), a 53-year-old man, was admitted to the hospital in May, 1943. He had been perfectly well until 2 hours prior to entry, when he noticed a sudden, sharp, right-sided pleuritic chest pain accompanied by dyspnea. Physical examination revealed classic signs of a right pneumothorax and was otherwise negative. Two x-ray films of the chest confirmed the presence of a 50 per cent pneumothorax on the right. An area of patchy density was described in the collapsed right upper lobe.

Examination of the blood revealed a red-cell count of 4,720,000, with a hemoglobin of 14 gm., and a white-cell count of 9000, with 79 per cent neutrophils, 18 per cent lymphocytes and 3 per cent monocytes. The blood sedimentation rate was 15 mm. per hour. Two urinalyses were negative.

The patient left the hospital against advice on the 6th hospital day before further investigation could be carried out.

He was readmitted 14 months later with a 10-week history of cough, right-sided chest pain radiating down the right arm, progressive weakness, anorexia and a weight loss of 25 pounds. Physical examination revealed a Horner's syndrome on the right, signs of a mass in the right upper lung and a mediastinal shift to the left. A large tender mass was palpated in the right flank. Laboratory studies were negative except for a moderate degree of anemia.

The patient went downhill rapidly and died 3 weeks after admission. Autopsy revealed a renal-cell carcinoma of the right kidney, with metastases to the left adrenal gland and right lung.

In this case the spontaneous pneumothorax undoubtedly represented the lung metastasis, and since renal-cell carcinoma tends toward solitary metas-

tases, it is interesting to speculate whether early diagnosis might have prolonged the patient's life.

Spontaneous Pneumothorax in Apparently Healthy Persons

Of the 36 cases in the second group 30, or 83.3 per cent, occurred in male patients. This predilection has been reported by all previous investigators. As stated above, there was an age range of three to fifty-three years, with an average age of twenty-seven years and one month. Table 2 shows the contrast of age incidence by decades between the two groups.

Of the 36 patients in the second group 21 were successfully followed for periods ranging from one and a half to twelve years. Of these, 2 had died of other causes: 1 of cirrhosis of the liver five years after the occurrence of the pneumothorax, and the other of acute yellow atrophy of the liver two and a half years after the original attack. Post-mortem examination of the lungs in the latter case was reported as negative.

Three patients had multiple recurrences — an incidence of 14.3 per cent (in other series a recurrence rate of 10 to 30 per cent has been reported[8]). One of these 3 patients had multiple attacks, estimated by the patient as numbering eighteen to twenty. Chest x-ray study was negative six and a half years after the original attack, and the patient was considered a candidate for the induction of a chemical pleuritis. One female patient had a total of seven recurrences and had a negative x-ray examination twelve years after the original attack. The third patient in this group had a total of seven recurrences. Between the fourth and fifth attacks he developed clinical and x-ray evidence of tuberculosis, and he died three and a half years after the first occurrence of pneumothorax. After the first four episodes the lung fields had appeared clear after re-expansion, and during the first and second admissions tuberculin tests had been negative in dilutions of 1:100. This patient represents the only one in the second group who was known to have developed tuberculosis. Kjaergaard[7] followed 49 patients of this type and found only 1 who developed tuberculosis subsequent to spontaneous pneumothorax. In a review of the literature Perry[9] could find a record of only 6 cases developing tuberculosis after a benign spontaneous pneumothorax.

One patient had a typical attack of spontaneous mediastinal emphysema 3 years after the first occurrence of pneumothorax and was alive and well nine years later.

Treatment

All patients were treated with bed rest and symptomatic medication to relieve pain and cough. Aspiration of air to relieve dyspnea was done in 3 cases. Whenever possible, appropriate therapy was directed toward the underlying condition in patients in the first group. Patients with tuberculosis were transferred to sanatoriums shortly after admission. Hospitalization of patients in the second group varied from two to thirty-six days, with an average stay of eleven days. There was no immediate mortality in this group. Four patients in the first group expired during the hospital stay.

Summary and Conclusions

One hundred cases of spontaneous pneumothorax in patients admitted to the Boston City Hospital between 1934 and 1943 are presented. Of these, 64 patients, with an average age of forty-six years and one month, had underlying pulmonary disease, of which tuberculosis constituted 59 per cent.

Thirty-six cases occurred in apparently healthy persons with an average age of twenty-seven years and one month, 21 of whom were successfully followed for periods of one and a half to twelve years. Three patients, or 14.3 per cent, had recurrences. One had a subsequent attack of spontaneous mediastinal emphysema. Another developed tuberculosis after four recurrences.

A comparison of the history and clinical signs and symptoms in the two groups is presented.

The occurrence of a spontaneous pneumothorax in a person over forty-five years of age should excite suspicion of an underlying pulmonary lesion. A case is presented to illustrate this point.

The prognosis in the apparently healthy person with a spontaneous pneumothorax is excellent from the standpoint of both immediate recovery and the subsequent development of tuberculosis.

Table 2. *Comparison of Age Incidence of Spontaneous Pneumothorax in Patients with Underlying Pulmonary Disease and in Apparently Healthy Persons.*

Age	Patients with Underlying Pulmonary Disease		Apparently Healthy Persons	
yr.	no.	percentage	no.	percentage
0- 9	0	0	1	2.8
10-19	4	6.3	7	19.4
20-29	9	14.0	17	47.2
30-39	12	18.8	5	13.9
40-49	10	15.6	5	13.9
50-59	13	20.3	1	2.8
60-69	11	17.2	0	0
70-79	3	4.7	0	0
80-89	2	3.1	0	0
Totals	64		36	

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STREPTOMYCIN TREATMENT OF BACTERIAL ENDOCARDITIS*

Report of a Case

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With the Technical Assistance of Mary Meyeserian||

BOSTON

A CASE of bacterial endocarditis due to a gram-negative organism belonging to the genus Hemophilus is reported for two reasons: it is one of the early reported recoveries following treatment with streptomycin — perhaps the first patient of this kind to recover without any other therapy; and recovery followed a shorter course of treatment than would ordinarily be planned.

CASE REPORT

S. K., a 9-year-old girl, entered the House of the Good Samaritan on June 28, 1946, complaining of fever of about 3 months' duration. Her birth and early development were thought to have been normal. At 4 years of age she experienced an attack of fever accompanied by migratory joint pain. From that time on she was thought to tire easily, to be short of breath, and to become blue on climbing a flight of stairs. The physician who referred her to the hospital first saw her when she was 6 years old. He observed her to be cyanotic, to have an enlarged heart by physical examination and by fluoroscopy, and to have a hemoglobin of 13.5 gm. Despite these findings she remained in fair health for the next 2 years.

On April 27, 1946, the patient returned to the physician's office complaining of fever of an indefinite duration. Examination showed her to be intensely cyanotic, with a liver edge palpable 4 fingerbreadths below the costal margin and with an enlarged spleen. She was admitted to another hospital 2 days later. At that institution the hemoglobin was 12.7 gm., the red-cell count 4,300,000, and the white-cell count 14,200. The heart was enlarged by x-ray study. Three blood cultures grew no organism. For 1 month of hospitalization the course was febrile, with daily oral temperature elevations to 102°F. The physical findings did not change. From discharge on May 24 until her admission to the House of the Good Samaritan she remained in bed at home, where she continued to run a fever. On one or more occasions during this period there were minor hemoptyses.

Physical examination disclosed a thin, pale child, who was small for her age and moderately cyanotic. The weight was 50 pounds. There was minimal clubbing of the fingers and toes. The heart was large, with a forceful, apical impulse for a maximum of 7 cm. from the midsternal line in the fourth intercostal space, 1.5 cm. outside the midclavicular line. Dullness to percussion was detected well out in the second and third left interspaces. There was a Grade IV to Grade V, rough, systolic murmur and thrill maximum in the first and second left interspaces. The murmur was well transmitted to the apex, neck and interscapular region and tended to mask the basal but not the apical heart sounds. There was a loud, diastolic, third heart sound, but no diastolic murmur. Arterial and venous cervical pulsations were present with the patient erect. The blood pressure was 125/80, and femoral pulsations were strong. The liver edge was felt 4 cm. below the costal margin but was not tender. The spleen was easily palpable. No petechiae were seen, nor were Osler's nodes demonstrated.

Examination of the urinary sediment revealed 15 to 20 red cells per high-power field. The red-cell count was 4,960,000, with a hemoglobin of 11.8 gm., and the hematocrit was 40 per cent. The white-cell count was 11,600. The corrected sedimentation rate by the Ernstene–Rourke method was 1.5 mm. per minute (normal, 0.05 to 0.40 mm. per minute). Agglutinations for brucellosis and typhoid fever were negative. The electrocardiogram was typical of extreme right-sided heart strain. Fluoroscopy showed the heart to be large, with a massive right ventricle and dilated main pulmonary artery, but small intrapulmonary branches and an inconspicuous aortic knob.

From admission until specific treatment was begun on July 19 the patient ran a fever, the rectal temperatures spiking daily to 103°F. at 4:00 p.m. and falling to 96°F. each morning at 8:00 o'clock. The blood was cultured on June 28, on July 1 and 2 and again just before treatment was started on July 19. In all, fourteen flasks were inoculated, and in every one there grew out a small, gram-negative, coccal bacillus.

TABLE 1. *Serum Levels after Single Intramuscular Injection of 250,000 Units of Streptomycin.*

DATE	TIME OF WITHDRAWING BLOOD SAMPLE	INTERVAL SINCE PREVIOUS INJECTION	SERUM STREPTOMYCIN LEVEL
		hr.	*units per cc.*
July 22	3:25 p.m.	3	20
	4:00 p.m.	½	66
	4:30 p.m.	1	50
	5:30 p.m.	2	20
	6:30 p.m.	3	10
July 23	12 noon	3	20

This micro-organism was studied in some detail by George E. Foley, of the Children's Hospital, Boston, who found that it presented the morphologic, cultural and biochemical characteristics of the genus Hemophilus. It did not agglutinate with *Haemophilus influenzae* antiserums, Types A through F. Its ability to grow in mediums without hematin (X factor) but not in those without yeast (V factor) was interpreted as being typical for *H. parainfluenzae*.[1]

Sensitivity of the organism to known concentrations of penicillin and streptomycin was determined on blood-agar plates rather than in dextrose broth, in which the organism grew very poorly. A control organism of known penicillin sensitivity (when tested in broth) was found to be inhibited with the expected concentration of penicillin on the blood-agar medium.

Growth of the organism was not inhibited by concentrations of penicillin as high as 10 units per cubic centimeter. Streptomycin inhibited growth in concentrations greater than 2 units and less than 4 units per cubic centimeter. These results indicated that in vitro the organism was resistant to penicillin but sensitive to concentrations of streptomycin easily obtainable in the blood. Table 1 shows that serum streptomycin concentrations from five to fifteen times that required to inhibit the organism in vitro were actually obtained during therapy.

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On July 19 treatment was started with 2 gm. of streptomycin daily, given in eight divided doses at 3-hour intervals by intramuscular injection. The course planned was to extend over a 14-day period, during which the patient was to receive a total of 28 gm. of the drug. The septic fever broke immediately after the first dose. Blood cultures taken 18 hours after the start of therapy, those made while on treatment and those taken as late as 2 months after the end of therapy showed no growth (Fig. 1).

The patient improved during the first 5 days of treatment until it became necessary to use a different brand of streptomycin. The second lot caused fever, with rectal temperatures sustained between 101 and 103°F. and local irritation so severe that treatment had to be discontinued after a total of only 13.5 gm. had been given in 6½ days. There was no other evidence of a toxic reaction to the drug.

After omission of therapy the temperature fell by lysis in 4 days. The patient improved steadily and uneventfully except for a small hemoptysis on July 28. She gained 13 pounds and seemed entirely well at time of discharge on November 24. Although the liver became smaller, the spleen remained palpable throughout hospitalization.

During convalescence the red-cell count rose to 5,750,000, the hemoglobin to 16.3 gm., and the hematocrit to 54 per cent, although with the disappearance of the signs of heart failure cyanosis became minimal. These high values supported the possible diagnosis of an underlying cardiac anomaly consisting of a right-to-left shunt. Consequently, the patient was referred to Dr. Lewis Dexter and his associates at the Peter Bent Brigham Hospital for study by venous catheterization. Dr. Dexter's findings were consistent with a high degree of pulmonary stenosis together with a small ventricular septal defect and probable overriding aorta. The Blalock operation was not advised by Dr. Dexter because the oxygen saturation of the peripheral arterial blood was found to be high (87 per cent).

The patient was well and active at the time of writing, 1 year after the completion of therapy.

Discussion

Gram-negative bacilli are only occasionally the agents causing bacterial endocarditis. Of the small proportion of endocarditides so caused most of the infections are by members of the genus Hemophilus. Thayer[2] implicated this group in 2.9 per cent of all cases of infective endocarditis. As in bacterial endocarditis due to the *Streptococcus viridans*, infection is always implanted on a congenital defect or previously damaged cardiac valve, and the clinical manifestations, course and prognosis of the untreated disease are the same with either organism.[2–5]

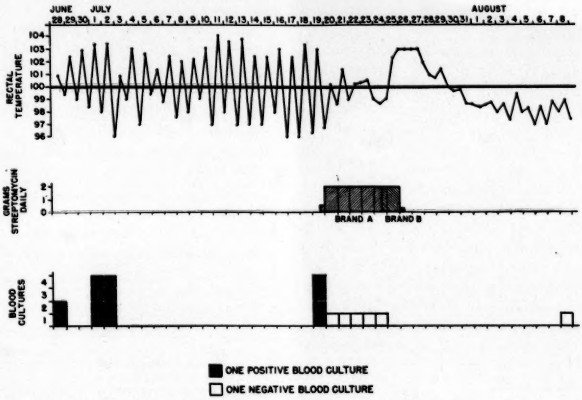

FIGURE 1. *Temperature, Streptomycin Dosage and Blood Cultures in a Case of Bacterial Endocarditis.*

Craven, Poston and Orgain,[3] in 1940, were unable to find a report of a case due to an influenzal or parainfluenzal organism in which the patient recovered.

Since 1941 apparent cures have been reported in 8 patients treated with sulfonamides and antibiotics.[4, 6–9] Of 2 cases treated at Mount Sinai Hospital, 1 was arrested with a sulfonamide alone, whereas the other responded to sulfapyridine and hyperthermia.[6] After each had proved ineffective alone, penicillin and sulfamerazine combined sterilized the blood of a patient reported by Priest and McGee.[7] Of 2 cases reported by Hunter and Duane,[8] 1 yielded to sulfadiazine after penicillin had failed. The second patient recovered after penicillin, sulfadiazine and streptomycin had been used.[8] Streptomycin may well have been the effective agent in this case, but unfortunately three blood cultures taken before streptomycin was started remained sterile.

More recently Hunter[9] added 2 cases from his own experience and 5 more supplied to him by Dr. Chester Keefer. In these 7 cases, 3 patients have survived. Each of the survivors received penicillin or a sulfonamide prior to or in conjunction with

streptomycin, although the latter was credited with the favorable outcome.

A much wider experience is available in the treatment with streptomycin of influenzal and para-influenzal infections of other systems. The drug has proved to be effective in meningitis, pulmonary disease, bacteremia and urinary-tract infection.[10–12] Unfortunately, its usefulness has been limited by the rapid development of organism resistance when the concentration of the drug at the site of the lesion is inadequate and by the toxic effects that have lately become apparent.

Deliberate attempts to increase the resistance of gonococci to streptomycin in vitro have resulted in tolerance by the organism of from 1900 to perhaps as much as 75,000 times the originally effective concentration.[13] This demonstration has been paralleled clinically with *H. influenzae* infections, as well as with infections due to other organisms.[14, 15] In these cases loss of therapeutic effect has been associated with a decreased sensitivity of successively isolated organisms. In 1946 Keefer[11] considered it advisable to maintain at the lesion a concentration of streptomycin from four to eight times that required to inhibit the organism in vitro so that infection could be eradicated before resistance to the drug developed. No patient in Hunter's[9] group recovered if a concentration greater than 8 microgm. of streptomycin per cubic centimeter was required to inhibit the causative organism in vitro.

The important toxic manifestation is severe and possibly permanent eighth-nerve damage, with not only vestibular dysfunction but [illegible] nerve deafness.[16] Damage increases with both the amounts of streptomycin given and the period of administration. Histamine-like reactions may be effectively treated with benadryl or pyribenzamine, and local irritation is not a problem with pure preparations.

It is apparent that high concentrations of streptomycin are desirable from the start, that if resistant strains appear, prolonged treatment may be useless, and that the longer the treatment, the greater the risk of vestibular damage and nerve deafness. If effective a short, intensive course should theoretically be ideal. Hunter recommends three or four weeks of treatment with 2 to 6 gm. of streptomycin daily, with the reservation that if the case is clinically favorable and nerve deafness is developing the drug may be stopped after two weeks. It is of interest that the patient in the case reported above recovered after only six and a half days of treatment.

Summary

Streptomycin was an effective agent for treatment in a case of endocarditis caused by a gram-negative organism belonging to the genus Hemophilus.

The causative organism was isolated and its sensitivity to the drug in vitro determined before treatment was started.

The concentration of streptomycin maintained in the blood was never less than twice and rose as high as fifteen times that required to inhibit the organism in vitro.

A short, intensive course of streptomycin eradicated the infection in this case.

We are indebted to George E. Foley and Commander L. A. Barnes, H (S), USNR, for their identification of the organism, and to Dr. Norman Pokorny, who diagnosed the disease and referred the patient for treatment.

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MALARIA*

Observations on Treatment with Chloroquine (SN 7618) and Combined Quinine and Plasmochin

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NUMEROUS excellent descriptions of the clinical symptomatology, course and response to quinacrine (atabrine) therapy of relapsing vivax malaria of Pacific origin have appeared in the last four years. Most and his associates[1] have described the effects on the relapse rate of combined quinine and plasmochin treatment. Similar but less complete studies have been made by Bianco and his co-workers[2] and others. Loeb,[3] Most et al.[4] and Faust[5] have described the early results of treatment with chloroquine (SN 7618). All these studies were carried out in the various military services, with the patients usually hospitalized throughout the entire period of therapy and follow-up observation. It was believed, therefore, that a longer post-therapeutic follow-up period of patients who had been living under ordinary civilian conditions would prove of value, and that general trends in the course of the infection might be of interest to the practitioner.

MATERIALS AND METHODS

During the year of July 1, 1946, to July 1, 1947, 125 patients with proved malaria due to *Plasmodium vivax*, all of Pacific origin, were admitted to the Veterans Administration Hospital, West Roxbury, Massachusetts. All had received suppressive quinacrine therapy while stationed in malarial zones, and most had been given various doses of quinacrine for prior clinical attacks. Once a positive smear had been obtained, either of two methods of treatment was offered. Those who desired as short a period of hospitalization as possible were treated with chloroquine diphosphate.§ The dosage was 1.0 gm. (4 tablets, each containing 0.25 gm. of the diphosphate) followed in eight hours by 0.5 gm. (2 tablets). A single dose of 0.5 gm. was administered on the second and third days of treatment. Most patients were discharged on that day, with instructions to take 0.5 gm. (2 tablets) every Sunday for five weeks. Out-patient follow-up physical examinations with smears for malarial parasites and an extensive symptomatic history were obtained every two months. If an unusual clinical finding such as a positive serologic test had been noted, the checkups were made on a monthly basis.

Patients who complained of over five recurrent attacks of malaria and those who were able to spend two weeks in the hospital were placed on the combined quinine-plasmochin regime as outlined by Most et al.[1] Plasmochin naphthoate, in 0.02-gm. doses, was administered every eight hours for fourteen days. Quinine sulfate was prescribed in 1.0-gm. doses every eight hours for one day followed by 0.6 gm. every eight hours for thirteen days. Repeated urinalyses, blood counts and electrocardiograms were performed to detect any evidence of toxic reactions to the drugs. The medications were given simultaneously. Fluids were forced during the acute relapse, ferrous sulfate was prescribed when any significant anemia was detected on admission, and the patients were restricted to no greater activity than a short walk to the dining hall or bathroom. Follow-up examination was identical to that described for patients treated with chloroquine.

RESULTS

Eighty-nine patients were followed for a period of six to twelve months, and the remainder for one to six months. Striking differences between the results of the two treatments were noted and are discussed separately. Because a veteran may receive greater compensation if a greater relapse rate is indicated, the relapses were divided into proved or laboratory relapses and symptomatic relapses with negative smears.

Twenty-six patients received chloroquine therapy. Within three months 9 had experienced repeated symptoms of an acute relapse associated with a positive smear for *P. vivax*. One patient relapsed seven, and 1 nine months after completion of this course of therapy. Ten patients were subsequently treated with quinine and plasmochin. The eleventh, a physician, experienced repeated relapses every three to five months, with an increasing interval between relapses. An additional 11 patients complained of slight fever and other minor symptoms suggestive of relapse, but self-medication with quinacrine was taken and subsequent smears were negative. The total failure rate of 84 per cent and laboratory rate of 42 per cent were essentially the same as those obtained with quinacrine. No toxic symptoms from the use of chloroquine were noted. Its effect on the acute relapse was as prompt as that of quinacrine. It was more pleasant for the patient

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§Furnished through the courtesy of Mr. Shepherd M. Crain, Department of Medical Research, Winthrop Chemical Company, Incorporated. It should be noted that the doses employed in this study differed from those given in the earlier reports on this drug, in which tablets containing 0.30 gm. of the base were administered. Only tablets containing 0.15 gm. of the base (0.25 gm. of the diphosphate) are now available.

to take, since it neither produced gastrointestinal irritation nor discolored the skin. No definite relapses occurred during the five-week period of suppressive therapy, although 2 patients stated that they felt sick every Saturday, just before taking the weekly suppressive dose.

Sixty-three patients treated with the combined quinine and plasmochin regime were followed for six to twelve months after completion of therapy. No case of a laboratory relapse occurred. Sixteen patients stated that they had experienced symptoms, which they interpreted as an attack of malaria — a symptomatic relapse rate of 26 per cent. One of these had persistent splenomegaly; 6 were subsequently admitted to the hospital for "malarial attacks," and negative smears were obtained. In some cases adequate cause for the fever was found in infection of the urinary or respiratory tracts, and the remainder were afebrile. No laboratory relapses occurred in an additional 40 patients followed for less than six months. All patients stated that they noted great improvement in their sense of well-being.

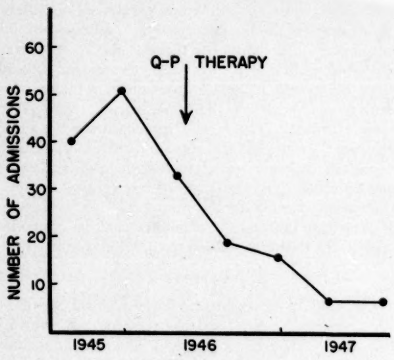

FIGURE 1. *Monthly Admission Rate, Averaged Quarterly, of Patients with Proved Vivax Malaria (September, 1945, to July, 1947).*

The toxic manifestations of plasmochin were not serious or severe. The principal toxic symptoms or signs observed were mild to severe epigastric burning, abdominal cramps and diarrhea. These symptoms most commonly occurred during and after the fifth day of therapy. Abdominal pain was severe enough in 2 cases to necessitate discontinuance of the medication for several doses before the treatment could be continued to completion. There was no relation of the severity of the gastrointestinal symptoms to other manifestations of toxicity. X-ray studies in several cases during this period of discomfort failed to reveal any gastric hyperperistalsis or intestinal spasm.

Circulatory signs and symptoms consisted of the appearance or disappearance of ventricular extrasystoles concurrently with the administration of the drug in 1 case. Cyanosis was rarely observed, as was the central-nervous-system symptom of "nervousness." No evidence of any hemolytic anemia was encountered.[6] It should be emphasized, however, that only white patients were treated and that they were kept on restricted activity.

The usual symptoms of quinine toxicity — namely, tinnitus, fullness in the head and ears and headache — were noted in minor degree and caused no interruption of therapy. One patient who gave a history of hypersensitivity to quinine was uneventfully treated with chloroquine.

Discussion

Our experience indicates that chloroquine is easier to administer to the patient and does not have the yellow-dye discoloration effect of quinacrine. Clinically, it was no more effective in preventing relapses than quinacrine. The combined quinine and plasmochin regime has proved as effective in reducing the relapse rate over a prolonged follow-up period as Most et al.[1] found it to be. It is expensive and takes time, and yet is effective in returning the nonworking patient to gainful employment. Under controlled observation no toxic manifestations of importance occurred. The abdominal cramps seemed to be relieved best by rest. Sedatives and antispasmodics were ineffective. We do not recommend the combination except under controlled observation and restricted activity.

It is interesting that all the patients with the proved cases of recurrent malaria admitted to the hospital, with 2 exceptions, came from the Pacific area — New Guinea and adjacent islands, the Solomons, Netherlands East Indies, Philippine Islands and Okinawa. The exceptions had been stationed in the China and India-Burma theaters. No patients from the Mediterranean or Caribbean theater were encountered. This is of diagnostic importance, since many patients from the latter theaters have been referred to the hospital with the erroneous diagnosis of malaria.

We continue to see patients who were last in a malarial zone a year and a half ago, entering with their primary delayed malarial attack. Many had lacked their usual sense of well-being since they returned from overseas and may have experienced slight attacks in the interim. Almost without exception these cases have not been recognized as malaria by physicians, and the patients were admitted to the hospital with diagnoses of fever of unknown origin or pneumonia. No cause for the lighting up of these dormant infections was elicited.

Conversely, the prophesied subsidence of the malarial attacks of Pacific origin after three or four years has been borne out by the admission rate. Figure 1 illustrates the monthly admission for proved malaria, averaged quarterly. The curve suggests a possible effect of the combined quinine and plasmochin therapy on the recurrence rate, since prior to July 1, 1946, many patients had been hospitalized two or more times, the admission rate thus being elevated. In addition, the patients admitted during the past six months had acquired the infection in 1944 or later. Certainly the bulk of those who contracted the disease in 1942 or 1943 are no longer experiencing symptoms that can be proved to be due to malaria.

Summary

Chloroquine (SN 7618) was as effective and better tolerated than quinacrine (atabrine) in acute malarial relapses or when used for suppressive therapy. It does not further reduce the relapse rate of malaria of Pacific origin.

The combined quinine and plasmochin regime, under controlled observation and restricted activity, affords a safe and effective means of markedly reducing the relapse rate.

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EXFOLIATIVE DERMATITIS DUE TO CODEINE*

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CODEINE has been in use as a narcotic since 1832,[1] when it was first extracted from opium. Chemically, it is the methyl ester of morphine[2] containing a phenanthrine nucleus.[3] Today it is used in massive amounts, especially in sanatoriums, and yet drug eruptions due to sensitivity to this agent are extremely rare. Seidmann[1] stated that up to 1943 only 10 such cases had been reported in the literature. Since then at least 2 additional cases have been reported. The following case is presented because of the severity of both the skin and systemic manifestations.

Case Report

A 34-year-old man was admitted to the hospital with a diagnosis of scarlet fever. The past medical history revealed that the patient had had the usual childhood diseases, a recurrent otitis media of a chronic nature and gonorrhea three times in the past 10 years. There was no allergic history. The family history was noncontributory. Six weeks before admission the patient had first developed a severe myositis of the shoulder, involving chiefly the trapezius muscle, for which he had received large daily doses of codeine, phenobarbital, salicylates and thiamine until the day of admission. About 7 days before entry he developed a mild generalized erythematous rash with a superimposed urticaria, which caused a great deal of itching. This was unassociated with fever, sore throat or photophobia and subsided after 2 days. The erythema and urticaria recurred, however, 4 days later in a severer form, and was associated with fever. The systemic review was essentially negative.

Physical examination revealed a well developed, well nourished man. There was a generalized macular erythematous rash, with numerous superimposed giant urticarial wheals from 2 to 8 cm. in diameter distributed over the entire body. Over the bridge of the nose and malar prominences, there was a small punctate papillopustular rash, which was apparently quite recent in origin. Examination of the ears revealed a perforated right drum. Otherwise the physical examination was negative.

The temperature was 104°F.

The patient was taken off all medication and treated symptomatically. He continued to run a septic type of fever for approximately 4 days, after which the temperature suddenly dropped to low-grade levels. By the 2nd hospital day the punctate pustular rash previously noted over the nose and malar prominences had spread to involve the entire face and upper portion of the chest but advanced no farther. On the 3rd hospital day the urticaria subsided, leaving large purpuric spots on the involved portions of the skin. Numerous small desquamating areas were also noted at that time on the lower arms and legs. Soon thereafter a generalized desquamation of flaky loose scales up to several centimeters in diameter developed. The patient also complained of marked diplopia and eyeball pain, which, however, subsided after 3 days without residual symptoms and without recurrence. It was noted that the patient was extremely sensitive to temperature changes, such as a very mild draft or changing of bedclothes, during which he developed a frank chill. There was a marked tremor of the extended hands as well as an intention tremor, which also subsided as the patient improved. On the 8th hospital day the corium layer of the hands and soles of the feet was shed in glove-like fashion similar to that seen in scarlet fever. The desquamating areas began to weep considerable amounts of serous fluid. This was followed by crusting and continued desquamation. About the 12th hospital day a secondary skin infection involving the antecubital fossa and legs developed. This was followed by a marked rise in temperature up to 104°F., with leukocytosis and marked regional lymphadenitis. The patient was placed on penicillin therapy (40,000 units every 3 hours) intramuscularly and tyrothricin locally to involved areas, after which the temperature dropped to normal limits within 5 days. Symptomatic therapy and penicillin prophylactically were continued. His condition gradually improved during the next month, although a great deal of desquamation was noted.

After convalescence it was thought advisable to determine the origin of the dermatitis. Patch tests with codeine, pheno-

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barbital, thiamine and sodium salicylate, both solution (1:1,000) and the powdered form of the drug being used, were performed. There was no reaction to these tests. The patient was then given intradermal injections of 1:10,000 of the same preparations at 1-week intervals. There was no reaction to salicylates, phenobarbital or thiamine. However, 30 seconds after the injection of codeine a giant urticaria at the site of injection about the size of the palm of the hand, as well as a generalized urticaria, developed. This subsided after eight hours. However, by the next morning there was a marked purpuric spot in the area of the skin test, as well as a fine punctate pustular rash involving the face similar to that observed on admission. At that time considerable concern was caused by the fear that a recurrence of the dermatitis had been precipitated. However, the rash entirely subsided within 48 hours without further complications. The patient was discharged on the 70th hospital day.

Repeated urinalyses during hospitalization were negative, with specific gravities ranging up to 1.028. Because of the diplopia a spinal tap was done, which was also negative, as were repeated blood cultures. Agglutination studies for typhoid, salmonella and the brucella organisms were also negative. Routine blood studies revealed a red-cell count varying from 4,500,000 to 5,000,000 during hospitalization. The white-cell count on admission was 8200 with 3 per cent eosinophils, 11 per cent lymphocytes, 2 per cent monocytes and 84 per cent neutrophils. By the 14th hospital day, during the height of the secondary infection, the white-cell count rose to 19,000 with 11 per cent eosinophils, 15 per cent lymphocytes, 6 per cent monocytes and 68 per cent neutrophils. On the 30th hospital day the white-cell count returned to normal, showing only 1 per cent eosinophils. On the day of discharge the white-cell count and differential were normal. The serologic findings were negative. Throat cultures revealed *Staphylococcus albus*. Cultures of the secondarily infected areas were positive for hemolytic staphyloccus. Repeated x-ray films of the chest were normal.

Discussion

Pollak[4] first described a case of pinhead-sized papulopustular eruption due to codeine in a one-and-a-half-year-old child who had been receiving codeine for some time in a cough mixture. This was similar to the presenting facial rash in the case reported above, except that in the former case the rash was mild and quickly disappeared after withdrawal of the drug without further complications.

An itchy erythematous rash due to codeine that was similar to the urticarial erythematous rash on the trunk and limbs in this case and that later cleared after mild desquamation was described by Von Essen[5] in a thirty-one-year-old woman.

The most frequent finding in reported cases has been an erythematous scarlatiniform eruption, which the case reported above also exhibited.[1–12] This manifestation was very well described and discussed by Scheer and Keil,[6] who reported such a case. In their patient the patch test was positive to a solution of codeine but was negative when the powder was used. Palmer's[3] patient also had positive patch tests to 1:100 and 1:1000 solutions.

Although patch testing is rarely of value in dermatitis medicamentosa, it was thought justifiable to attempt to determine the etiology of this patient's dermatitis in view of successful reports.[3, 6] However, patch tests employing both the powdered drugs and the 1:1000 solutions were negative. Intradermal skin tests using 1:10,000 solutions were then employed. These were negative for thiamine, sodium salicylate and phenobarbital, but there was a marked reaction to codeine. Scheer and Keil first noted that codeine injected intradermally gave a positive wheal in normal persons and that the intradermal test was valueless. We were not aware of this at the time we attempted to determine the etiology of this patient's difficulty. Although no deaths have been reported from codeine sensitivity, there seems little doubt that poor judgment was exercised in the use of intradermal skin tests in this case, since it is easy to imagine that a severe recurrence of the exfoliative dermatitis may have been precipitated by this procedure. However, the diagnosis seems well established in view of the recurrence, after the intradermal injection of codeine, of a generalized urticaria followed by a punctate papulopustular eruption of the face similar to the original eruption.

None of the previously reported cases have run such a toxic course, nor have the patients had so many and severe skin manifestations as this patient presented. These included pustular papules, erythema, urticaria, purpura and eventually generalized exfoliative dermatitis. The patient was desperately ill for approximately a month, and only by the use of antibiotics for the control of secondary infections and by considerable nursing care was he saved. The marked transient eosinophilia has been observed previously in this condition,[1, 9] but as noted above is not a common finding in drug eruptions.

Summary

A case of exfoliative dermatitis due to codeine is reported. The rash was manifested by a papulopustular eruption of the face and generalized macular erythematous rash with superimposed urticaria, which was followed by weeping in some areas and generalized desquamation. For forty days the patient ran a severe course complicated by secondary infection. After recovery a skin patch test was negative but the intradermal injection of a 1:10,000 solution of codeine caused a generalized urticaria and mild manifestations of the original picture. This was thought to be sufficient evidence to establish the etiology.

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MEDICAL PROGRESS

DIABETES (Concluded)

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PREGNANCY IN DIABETES

Pregnancy in diabetes continues to interest Dr. Priscilla White,[32] and in an article presented before the Third Congress of Obstetrics and Gynecology, her conclusions were brought up to date:

> The typical course of a diabetic pregnancy as seen in diabetic clinics is the following one: from conception to term the pregnancy has a 50 per cent chance for survival and terminating in a live birth. If pregnancies of diabetics are studied from viability on, the chances for success increase to 65, rarely to 75 per cent. (The expected fetal survival at present is better than 90 per cent.)

The importance of vascular disease is stressed:

> Although fetal survival is possible with advanced arteriosclerosis, a review of our patients who had unexpected repeated failures showed that when arteriosclerosis was so advanced that the arteries of the pelvis were calcified (30 cases), the chances for fetal survival were poor, 10 per cent. In 16 cases where every form of treatment we know was included, the survival rose to 19 per cent. Calcified pelvic vessels not revealed in the pre- or early pregnancy screening plates have been revealed in from 6 to 12 months after failures or stormy pregnancies. Intimal disease favoring occlusion — characteristic of diabetes — is inferred to be present before the calcium is deposited.
>
> Seventy-five per cent of our patients are delivered by Cesarean section, performed under spinal anaesthesia without preliminary sedation. Spontaneous normal deliveries are also conducted under spinal anaesthesia and with minimal sedation.

For details of treatment of both mother and child, the original article must be consulted, but the following is a brief summary:

> The management of diabetes includes the prescription of diets high in carbohydrate 180 to 250 grams, high in protein 2.0 grams per kilogram of body weight, and fat to complete the caloric prescription of 30 calories per kilogram.
>
> Multiple doses of insulin protect the patient from the ketosis consequent to the low renal threshold for glucose and avoid hypoglycemia.
>
> The treatment of the disturbed chemistry includes the use of ammonium chloride in doses of 4 to 8 grams daily, acid ash, high protein diets. Sodium is restricted. The most important part of the treatment is the substitutional hormonal therapy.
>
> Various routes of administration, types of therapy, durations of treatment have been employed but the best results in my experience have been with early and continuous stilboestrol and proluton intramuscularly. The present form of treatment is as follows:

Week of Pregnancy	Stilboestrol mg. daily	Proluton mg. daily
Up to 20th	5	5
20–24	10	10
24–28	15	15
28–32	25	25
32–38	50	50

> Regulation of stilboestrol is controlled by serum levels of chorionic gonadotropin and proluton by urinary determinations of pregnandiol.

METABOLISM OF CARBOHYDRATE AND FAT

An excellent summary of the work of the Coris and their associates at Washington University, St. Louis, was given by C. F. Cori[33] in his Harvey Lecture. It will be recalled that from these studies it became apparent that at least one site of action of insulin in the body is at the point at which glucose is admitted to the metabolic system by conversion to glucose-6-phosphate. This conversion of glucose takes place by reaction with adenosine triphosphate under the influence of a sulfhydryl enzyme, hexokinase. The Coris found that the hexokinase reaction was inhibited by anterior pituitary extract and that insulin opposed this inhibition. Insulin had no direct effect upon the reaction. Although not all the known facts can be fitted easily into the proposed scheme, a convincing demonstration of one site of action of insulin is now available. Stetten[34] regards Cori's work as of great significance and emphasizes the fact that once glucose has been phosphorylated, many pathways are open to it: it may be converted to glycogen or to fat, or it may be oxidized. Stetten and his co-workers[35] showed that in the well nourished rat, only about 3 per cent of the glucose ingested is converted to glycogen, whereas about 30 per cent (ten times as much) is consumed in the manufacture of fatty acids. More and more it is coming to be recognized that the metabolism of carbohydrate, protein and fat is not independent but that all three contribute to a common

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metabolic pool to which active fragments are constantly being added and withdrawn. Investigation along this line is for the first time possible through the use of isotopes by means of which individual molecules can be labeled and traced through the body.

Diabetes Section of the United States Public Health Service

The Diabetes Section of the United States Public Health Service was formed in recognition of the increasing public-health aspects of diabetes. There is a growing diabetic population, and indications are that only about half the patients have been found. To avoid complications of the disease, efforts must be made to find the others early and to start their education. The objectives of the Diabetes Section are to demonstrate the application of public-health measures in the early detection of the disease and to stimulate, encourage and support research in all aspects of diabetes, including the development of new laboratory methods and technics.

Among the accomplishments of this section have been the Oxford Diabetes Survey cited above and two diabetes units. One is established in co-operation with the Florida State, Duval County and City of Jacksonville Health Departments. The second unit works in co-operation with the Commonwealth of Massachusetts and the Town of Brookline Health Departments. The project includes early detection of cases and dissemination of information about diabetes to the diabetic patient and to the public. Patients with newly discovered diabetes are referred to their family physicians for further study and treatment.

A new rapid screening test for blood sugar — described below — has been devised. Exhibits on diabetes have been presented at meetings of the American Public Health Association and sectional medical meetings and in co-operation with the American Diabetes Association at the annual meeting of the American Medical Association in 1947. Educational material is being prepared for general-population groups, health departments and the practicing physician in co-operation with the American Diabetes Association.

New Rapid Blood Sugar Tests

The Benedict test affords a simple and convenient method by which not only physicians but also diabetic patients may test the urine for sugar. Modifications such as the "Clinitest" and "Galatest" allow for even greater speed and convenience. It would be of tremendous advantage to all concerned if simple and quick methods were available also for the determination of the blood sugar. Some progress in this direction has recently been made. Hagedorn and his collaborators[36] have devised rapid modifications of their ferricyanide method, including a procedure in which most of the reagents are provided in tablet form. A bedside method for the rapid determination of the approximate sugar content of the blood has been worked out by Leech and Woodford.[37] In this procedure, which requires a minimum of equipment and laboratory experience, blood proteins are precipitated by means of zinc hydroxide and the concentration of sugar in the filtrate determined by use of Sumner's dinitrosalicylate reagent. By either of these methods a blood sugar determination may be made within five minutes of the time of collection of the blood.

The third new method, developed by the Diabetes Office of the United States Public Health Service,[38] is particularly suited for rapid, large-scale screening tests in surveys and other studies of large population groups. The procedure is based on that of Hagedorn, but all reagents are in tablet form and the steps requiring experience in chemical technics and all fluid reagents have been eliminated. Within five minutes a sample of blood (0.1 cc.) can be classified as having above or below a certain glucose concentration.

With these new tests public-health departments have available means of early case finding, and the practicing physician can be materially aided in the better care of his diabetic patients.

Alloxan Diabetes

In previous years, attempts have been made to include in the progress reports[39] all references that have appeared on the subject of alloxan diabetes. The present article attempts to include all published reports on this subject since the previous summary in April, 1946. The subject has been extensively reviewed elsewhere.[40–43]

Chemistry

The chemistry of alloxan has been reviewed by Chen.[44] The diabetogenic action continues to be limited to alloxan and a few very closely related chemicals that may well change into alloxan once they are introduced into the body.

Brückmann and Wertheimer[45] report that n-methyl, ethyl and propyl alloxans, as well as alloxantin, dimethyl alloxantin, diethyl alloxan, dialuric acid and methyl dialuric acid, produce diabetes when injected into rabbits. Others[46–48] have shown that various ones of these compounds are diabetogenic, and Hidy[46] has stressed the fact that the intact pyrimidine ring is essential for the diabetogenic activity of any chemical compound such as alloxan.

Tipson and Ruben[49] claim that alloxan or its reduction product is present in the liver of normal animals and also describe their "purple" test for alloxan.[50] Karrer et al.[51] report a very sensitive test for the detection of alloxan and claim that this method will detect 0.5 γ of alloxan per cubic centimeter of aqueous solution. Using this method, however, they were unable to detect any alloxan in the serum or urine of diabetic patients.

The experiments of Iyengar[52] suggest that alloxan experimentally acts as an activator for insulin.

Physiology

In addition to the rabbit, rat, dog, monkey, pigeon and turtle, diabetes has been produced with alloxan in sheep,[53, 54] hamsters[55] and cats.[56]

Shipley and Rannefeld[57] showed that the injection of small subdiabetogenic doses of alloxan could irreversibly alter the functional reserve of the islet-cell tissue, as demonstrated by the glucose-tolerance test. Animals so treated if then given anterior pituitary extract developed a markedly increased blood sugar.

With ordinary diabetogenic doses of alloxan there is complete functional recovery from initial kidney damage.[58] Duffy[59] found that the dose of 200 mg. of alloxan per kilogram of body weight intravenously in rabbits resulted in death in many of the animals. Some of those that survived, however, developed diabetic cataracts.

Lazarow and Palay[60] found the intravenous injection of 40 mg. of alloxan per kilogram of body weight in rats a satisfactory method of producing diabetes mellitus. The intraperitoneal route required larger doses.

The withdrawal of all foods from adult rats for a period of forty-eight to sixty hours before the injection of alloxan renders the animals more susceptible than the nonfasted animals to the diabetogenic action of alloxan.[61] According to Houssay and Martinez[62] a low-protein or high-lard diet increases the rat's susceptibility to alloxan. The high-lard diet, however, loses its effects if methionine, thiouracil or coconut oil is added.

Levey and Suter[63] claim that the administration of ascorbic acid to rats increases the diabetogenic action of low doses of alloxan if the vitamin is given within one minute before the administration of alloxan. It has been stated that ketosis has been produced in alloxan-diabetic rats by means of a diet high in niacin.[64]

The initial hyperglycemia followed by temporary hypoglycemia that follows the injection of alloxan and precedes the onset of true diabetes has been discussed again.[65] Goldner and Gomori[66] present further evidence to support the hypothesis that the secondary hypoglycemia following the injection of alloxan is pancreatic in origin.

Canzanelli[67] found that, in vitro, alloxan has no direct effect upon liver glycogenolysis, and these findings therefore oppose the concept that the initial hyporglycemia of alloxan diabetes is a result of an effect of alloxan on the liver. It has been shown that alloxan inhibits muscle glycolysis and that this inhibition can be reversed by the addition of cysteine.[68]

The glycogen reserve of the muscles and of the liver in alloxan-diabetic rats has been approximately doubled by the administration of insulin.[69] Weber[70] found that the glycogen content of the liver after twenty-four hours of fasting was higher in alloxan-diabetic rats than in normal rats, whereas the glycogen content of the muscles was lower.

Franks et al.[71, 72] believe that the rise in the plasma inorganic phosphates of alloxan-diabetic rats during diabetic coma is due to a breakdown of the liver organic phosphates associated with a deficiency of insulin. The acid and alkaline phosphatase activity is significantly increased after the development of alloxan diabetes in rats according to Drabkin and Marsh,[73] and the administration of insulin produces a decrease in the activity of both acid and alkaline enzymes.[74]

Dogs made diabetic with alloxan have a more severe diabetes and require much higher doses of insulin than dogs made diabetic by pancreatectomy, according to Thorogood and Zimmerman.[75] Although some believe that this results from decreased food absorption since the digestive enzymes are decreased in amounts, these workers postulate the possibility of a second hormone from the pancreas, the absence of which allows the diabetes to become more severe and predisposed to ketosis.

Foglia et al.[76] showed that depancreatized rats that later receive a diabetogenic dose of alloxan develop after the administration of glucose a hyperglycemia, which is more acute and of longer duration than when rats that have been depancreatized alone are given glucose.

The secondary transitory hypoglycemia that follows the injection of alloxan into dogs is markedly delayed in dogs in which a vagotomy-thoracosympathectomy operation has been performed, according to Shipley and Beyer.[77]

Kendall and his associates[78] report a transitory period of hypercholesterolemia and hyperlipemia during the early stages of severe diabetes in rabbits injected with alloxan.

In 20 of 30 rabbits injected with alloxan by Herbut et al.[79] a very severe periportal necrosis of the liver occurred. The feeding of reduced iron to 2 diabetic and 2 controlled rabbits for two and a half weeks resulted in the deposition of iron in the liver and other organs. Attempts are being made to produce hemochromatosis by this method.

Rabbits made diabetic with alloxan that become pregnant have abortions, or premature delivery in half the experiments.[80] No evidence of an increased birth weight among the fetuses in diabetic rabbits was found, however. In rats made diabetic with alloxan, the pregnancies reach full term and result in the birth of healthy fetuses with normal birth weights. Injection of alloxan into pregnant animals appears to have no ill effect on the fetuses.

Prevention

Soon after it was proved that alloxan could produce diabetes in animals attempts were made to find substances that would prevent its diabetogenic

action. This was quite logical, for if alloxan had anything to do with the etiology of diabetes in human beings it would be quite important to find some substance that would prevent its action. It has been known for a long time that alloxan has an especial affinity for the sulfhydryl group, and Lazarow[81] has shown that, if large doses of glutathione or cysteine are intravenously injected into rats immediately before the injection of a diabetogenic dose of alloxan, diabetes is prevented. If, on the other hand, these substances are given one minute after the injection of alloxan only partial protection results. If the injection is made three or four minutes after the injection of alloxan no protection is seen.[82] Recently, it has been shown that BAL (British Anti-Lewisite) also prevents the diabetogenic action of alloxan in rats,[83–85] presumably because it too is a sulfhydryl compound.

Banerjee[86] found that 100 mg. of nicotinic acid per kilogram of body weight injected intravenously and followed by a like dose of alloxan protected 5 rabbits from diabetes. When doses of 200 mg. per kilogram were used, however, 2 of 3 rabbits developed diabetes.

Clamping the kidney vessels in the dog before the injection of alloxan prevents the development of diabetes according to the report of Jimenez-Diaz et al.[87] Other workers found that clamping the renal pedicle of rabbits or rats did not prevent the diabetogenic action of alloxan or the histologic changes in the islets of Langerhans.[88–90]

Walpole and Innes[91] found that ligation of the main pancreatic duct in rabbits prevents the action of alloxan, but no other reports supporting or rebutting this finding have yet appeared.

It has previously been reported that the injection of adrenalin intraperitoneally before the injection of alloxan prevented diabetes.[92] LeCompte and Bailey[89] found that the injection of small quantities of epinephrine intraperitoneally into rats produced a marked constriction of the capillary and small blood vessels of the intact pancreas, which could be seen microscopically. It is presumably the vasoconstriction that keeps the alloxan from reaching the islets of Langerhans and prevents the diabetes.

It has been suggested that pentnucleotides act as an antagonist to alloxan in the rat.[93]

Influence of Endocrine Glands

Gaarenstroom et al.[94–96] report that extirpation of the hypophysis in animals already made diabetic with alloxan leads to a marked decrease or even total disappearance of glycosuria and a fall in the blood sugar, in fasting animals. After administration of sugar, the blood sugar rises again to high levels.

Bailey and his co-workers[97] showed that if rats were hypophysectomized and then given alloxan, diabetes developed but was much milder than that in control animals given alloxan alone.

Houssay and his associates[98] have studied the relation of the thyroid gland to alloxan diabetes quite extensively. They report that thyroidectomized rats show a greater resistance to the diabetogenic and toxic action of alloxan than control animals and that thiouracil-treated rats show even greater resistance to alloxan.

Experimental hyperthyroidism produced by the administration of thyroid extract increases and thyroidectomy decreases the sensitivity of rats to the action of alloxan.[99] Dogs with transitory diabetes as a result of the injection of alloxan develop permanent diabetes when they are treated with thyroid extract,[100] but the administration of thyroid extract does not produce diabetes unless the islets of Langerhans have previously been injured. A very unusual finding was that thyroid treatment of pancreatectomized rats in which diabetes had already become incipient caused its complete disappearance. In spite of continued treatment, however, diabetes reappeared in a third of the animals. The nontreated controls all eventually became diabetic.[101]

Suarez Soto[102] also produced so-called "metathyroid diabetes" by administering thyroid extract to dogs whose pancreases had been handicapped by the administration of small doses of alloxan.

No amelioration of alloxan diabetes was found when rats were treated with diethyl stilbestrol.[103]

Janes and Friedgood[104] reported that when alloxan-diabetic rats were adrenalectomized a marked reduction or complete disappearance of diabetic symptoms resulted. On further study of this problem, however, they found that the amelioration of the diabetes following an adrenalectomy was associated with a lowered food intake rather than the direct results of the adrenalectomy.[105]

Pathology

The pathology of alloxan diabetes has been described in a most complete article by Duff.[106] Two new findings have been reported in the last year. Duff et al.[107] observed moderate to extreme hydropic degeneration of the pancreatic ductules and islets of rabbits made diabetic with alloxan after several months of diabetes. Such changes were detected as early as forty-five days and were never absent after ninety days, provided the average fasting blood sugar level was 303 mg. per 100 cc. or higher. These hydropic degenerative changes, both in the ductules and in the islets, are reversible if the diabetic state is treated with insulin.

Proliferative changes have been described by Di Pietro[108] in the centroacinar cells of the pancreas and the intracanalicular ducts.

Grossman and Ivy[109] believe that the vacuolization of the intralobular duct cells of the pancreas, along with their finding of decreased responsiveness to secretin, suggests that the small duct cells participate in the formation of pancreatic juice.

Clinical Considerations

The clinical implications of alloxan diabetes have been summarized by Bailey and LeCompte,[110] and the relation between experimental and human diabetes has been compared by Gale.[111] It has been pointed out that alloxan is a chemical with dangerous toxicity and its use in man at present is ill advised.

Since alloxan destroys the islets of Langerhans it was quite natural that it has been used in the treatment of hyperinsulinism. Talbot and Bailey[112] administered alloxan to an eight-month-old baby with the clinical and laboratory findings of hyperinsulinism, with somewhat encouraging results. This was done only after careful surgical exploration had failed to reveal any evidence of a pancreatic adenoma. The authors warn of the extreme dangers in the use of this drug.

The danger associated with the administration of alloxan in human beings has been well illustrated in a case of islet-cell carcinoma with extensive metastasis in which alloxan had been used as a last resort.[113] After three injections of alloxan the patient developed acute yellow atrophy and died with extensive liver necrosis.

Conn[114] reports that alloxan may destroy the normal islets of Langerhans in the pancreas. In the treatment of a case of hyperinsulinism with alloxan, no effects were noted on the pancreatic islet-cell adenomas, but the normal islet cells were damaged and the patient developed diabetes after the islet-cell carcinoma had been removed surgically. A biopsy of the pancreas in this case confirmed islet-cell damage.

Another case of islet-cell carcinoma of the pancreas with liver metastasis was treated with alloxan by Flinn et al.,[115] but no clinical effect from the alloxan was observed.

Uric acid diabetes is reported by Griffiths[116] of the Australian Institute of Anatomy, Canberra, Australia, as having been produced experimentally in rabbits. Recognizing that diabetogenic doses of alloxan, as well as ninhydrin (though nondiabetogenic) lower blood reduced glutathione levels in rats appreciably, he administered uric acid parenterally with the thought that it might exert a diabetogenic action under such conditions. Intraperitoneal injections of 1 gm. of uric acid per kilogram of body weight into these deficient animals caused an initial hyperglycemia lasting about eight hours. Later, despite food, the animals remained hyperglycemic, and glycosuria persisted for the next four or five days. The blood sugar response resembled that which follows an injection of alloxan.

* * *

The growth of interest in diabetes continues. Associations have been formed in the United States, England, France, Denmark, Belgium, Holland, New Zealand and Australia. In England and France publications for the lay public are issued, appearing in three or four issues yearly. The American Diabetes Association inaugurated such a policy beginning with the issuance of the *ADA Forecast* in January, 1948. This blue-covered magazine has been designed with great care. It is especially to be commended because there are no advertisements. I am sorry not to feel at liberty to disclose the sponsors of the publications, who have had so much to do with making their timely appearance possible. *Diabetes Abstracts* and the *ADA Forecast* are certainly very forward steps in the dissemination of knowledge of diabetes for doctors, patients and the public and surely cannot but result in a notable advance in treatment.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 34141

PRESENTATION OF CASE

A seventy-one-year-old man was admitted to the hospital because of orthopnea and ankle edema.

Ten years before entry he was treated in the Out Patient Department for late syphilis. Because of his age he was given bismuth only, and the blood Hinton test became negative. An x-ray film of the chest showed an enlarged heart and a tortuous aorta, with calcification of the aortic knob. Six years before entry he began to have dyspnea on exertion, and physical examination revealed an enlarged heart, with a regular rhythm, a soft apical systolic murmur (Grade II) and a soft aortic diastolic murmur (Grade I). He was digitalized and took digitalis irregularly ever since. The blood pressure was 140 to 150 systolic, 60 diastolic, the pulse 75-85, and the serologic tests for syphilis had been persistently negative. During the two weeks prior to admission he had severe dyspnea, with orthopnea and dependent edema.

Physical examination revealed a slightly cyanotic and icteric man. The neck veins were distended. There were fine, scattered rales in both lungs. The heart was enlarged, with the apex in the sixth space in the anterior axillary line. There were an aortic systolic (Grade II) and a diastolic (Grade I) murmur. The liver was enlarged and tender, and there was pitting edema of the lower legs.

The temperature was 100°F. (rectal), the pulse 100 (irregular), and the respirations 24. The blood pressure was 145 systolic, 60 diastolic.

The white-cell count was 9300, with 70 per cent neutrophils. The hemoglobin was 13.5 gm. A van den Bergh reaction was 0.9 mg. per 100 cc. direct, and 4.2 mg. indirect (later 0.9 mg. direct and 2.1 mg. indirect). A cephalin-flocculation test was negative (later, +++ in forty-eight hours). The nonprotein nitrogen, total protein and prothrombin time were within normal limits. Routine urine and stool examinations were negative.

An electrocardiogram showed auricular fibrillation and ventricular complexes arising from many different ectopic foci. A chest film demonstrated an enlarged heart of aortic configuration, with calcification in the aortic arch, and congestive changes in both lungs.

The patient was treated with digitalis, ammonium chloride, mercuhydrin and a low-sodium diet. Later, in view of the electrocardiographic findings, the digitalis was discontinued, and he was carried on 0.2 gm. of quinidine daily. A good diuresis was obtained, and the pulse steadied to 70 to 80 per minute. However, he began to have anorexia, nausea and right-upper-quadrant tenderness attributed to distention of the liver capsule. One week after admission he suddenly developed pain in the right upper arm, which became cold, blue and pulseless. He was given spasmalgin and prepared for immediate embolectomy. However, in the interval the embolus passed farther down the arm, and operation was postponed. He was put on dicumarol and heparin, and the arm finally regained its normal circulation. The prothrombin time increased to 65 seconds (control, 17 to 18 seconds), and the clotting time to 32 minutes. Two weeks after admission he developed repeated vomiting, which subsided the next day. He was given digifolin (1 cat-unit intramuscularly every other day) as well as the quinidine. He continued to have abdominal discomfort of varying severity without localization or tenderness and with negative x-ray studies. Four weeks after admission he suddenly had pain in the upper part of the abdomen and lower portion of the chest, restlessness, cold, clammy, dusky skin and a slow, irregular, weak pulse. The blood pressure was 80 systolic, 60 diastolic. There were a few rales in both lung bases, and the abdominal peristalsis was normal on auscultation. An electrocardiogram showed a rate of 65, a PR interval of 0.22 second, marked widening of the QRS complexes (0.29 second) and high T waves. The white-cell count was 19,200. Two hours later two examiners noted absent abdominal peristalsis. Both dicumarol and quinidine were discontinued. By noon the patient was much improved, ate well and had two stools. On the following day the white-cell count was 9800, the nonprotein nitrogen 67 mg. per 100 cc., and the prothrombin time 36 seconds. The urine was normal, and the stools gave a ++ guaiac reaction. A few days later an electrocardiogram showed a more normal rhythm and rate, and a less prolonged QRS complex (0.16 second). A stool was negative for guaiac. The patient was again given dicumarol, and the epigastric distress returned, especially after the ingestion of food. He developed rapid fibrillation, with an apex rate of 120 per minute. He was given purodigin, and the pulse rate diminished to 84, and the pain subsided. He died a few hours later, one month after admission.

DIFFERENTIAL DIAGNOSIS

DR. WYMAN RICHARDSON: I always wonder how the experts grade murmurs, and, also, I always suspect that a soft murmur means a faint one, and a

harsh murmur, a loud one; but I am not sure of all this.

I call attention to the fact that about three quarters of the bilirubin in this case was protein bound. I have called attention many times at these conferences to the fact that indirect bilirubin by the van den Bergh method means the total amount, including both that which requires the addition of alcohol and that which needs no addition of alcohol. Is that correct, Dr. Mallory?

DR. TRACY B. MALLORY: It must be.

DR. RICHARDSON: The direct test measures bilirubin that is not protein bound, and the indirect that which is due to protein-bound bilirubin. The finding in the case under discussion shows a slight increase of the blood bilirubin, most of which is due to protein-bound bilirubin. This is the significant point. One would expect to find some hemolytic process rather than an obstructive or intrahepatic process, although I do not think one can depend too much on this test.

The cephalin-flocculation test I am inclined to disregard, although probably I should not do so.

The nonprotein nitrogen at the time of entry was normal but later became elevated.

Digitalis was omitted — I suppose because of the ectopic beats and the suggestion of an irritable myocardium. Quinidine was given in small doses. It surprises me that, if the drug were used at all, more was not used. That amount may have been considered sufficient to prevent a sudden arrhythmia.

The clotting time may not be increased even though the prothrombin time is increased; but when the prothrombin time gets as high as that in the case under discussion, there is usually an increase in the clotting time too.

In the blood examination nothing is said about the distribution of the cells, and I have said much too much at these conferences about blood smears so that I will not say any more.

I think it is likely that the patient died of gastrointestinal hemorrhage. I want to say a few words about the use of anticoagulants. I am sure that I am a "stick-in-the-mud" regarding medicine and probably I am ultraconservative, but I should like to point out that when one uses anticoagulants and produces a prothrombin time of 65 and a clotting time of 32 minutes, one is adding a serious risk to the condition that the patient already has. I am not saying that anticoagulants should not be used when they are indicated. In some cases the calculated risk may be taken. But it seems to me that the pendulum has swung too far. I think it is fair to point out that a patient with a clotting time of 32 minutes is in constant danger of having a major vascular accident or major hemorrhage, as we know from our contact with hemophiliac patients. There is a patient on the surgical wards now with a peculiar type of bleeding and a clotting time of 32 minutes, and everyone is trying to bring that down. I do not want to go into the field of anticoagulants in phlebothrombosis, but I do think that we are going to find more and more cases in which increasing the prothrombin time has led to serious catastrophe or near catastrophe and in which the risk is not being clearly met. I am not doubting the integrity of those who use it and report on it, but it takes several years for the dangers to become apparent. Its use may have been justified in this case. This is the end of the sermon. I give it now, because I shall probably be wrong about this case and would not dare to talk about it afterwards.

What was this episode when the patient suddenly had upper abdominal pain? That is where the problem lies in this case. He became restless and had cold, clammy skin, a peculiar change in the electrocardiogram and an increased white-cell count. But in two hours he was very much better. What could have been the cause of this? My first and final thought was that he had a ruptured vessel, probably an artery. One might think of a pulmonary embolism. Why was it not a pulmonary embolism? It could have been, but it seemed to me to be rather a too rapid recovery. The white-cell count seemed to return to normal too rapidly. The same statement holds true for a ruptured viscus. If a viscus had ruptured into the abdominal cavity, I do not believe that the patient would have improved so much in two hours. The white-cell count of only 9800 may have represented a reaction to severe infection. I am unable to rule it out, but I doubt very much that it was infection. It may have been a hemorrhage into a closed cavity, such as rupture of an aneurysm, and that is a possibility that I cannot rule out. The thing that made me think of hemorrhage into the gastrointestinal tract was that he had had a great deal of abdominal pain, and something happened to intestinal peristalsis. I thought that loops of bowel might have been distended with blood. The nonprotein nitrogen rose to 67 mg. per 100 cc., which did not seem explainable on the basis of shock because he did not appear to be in shock except for a very short period. One further explanation of the attack could be a coronary occlusion, with myocardial infarction. That is about all I can do except to say what the trouble was in the first place. He might have had a syphilitic aortitis. I think the evidence is against that because of the negative blood Hinton test. I assume that a Hinton test was done, although it is not mentioned that it was done in dilution and there may have been a so-called prezone phenomenon; if it were done in dilution, it would finally show up positive in the smaller dilutions.

DR. MALLORY: We know that the blood Hinton test was positive at one time and eventually became negative under treatment.

DR. RICHARDSON: I am taking the diagnosis of syphilis for granted. The problem is whether the

patient had syphilitic aortitis on admission; if so, the chances are that he would have shown a positive blood Hinton reaction. I do not believe that one can rule aortitis out, however.

He may have had subacute bacterial endocarditis. There seems to be little to suggest that disease other than the emboli. With this vascular setup he might, of course, have had periarteritis nodosa, which we frequently talk about at these conferences; I see nothing that points to it.

I have already mentioned the question of massive pulmonary embolism. He may have had that to start with, and the whole process may have been due to thrombosis of the pulmonary circuit. There does not seem to have been a cor pulmonale; the heart failure seems to have been more diffuse.

The sudden death, I suppose, may well have been a true cardiac death, and the whole thing cardiac from start to finish. I will postulate, however, that the underlying disease was arteriosclerotic — that the patient had a calcareous aortic valve, with coronary insufficiency, possibly associated with interference with the coronary intake at the coronary ostia, and that he had pulmonary infarction. I will explain the jaundice on the basis of the absorption of blood pigment from a fairly large infarction. I think he had, undoubtedly, auricular thrombi or, possibly, mural thrombi to account for the systemic circulatory embolism (unless one wants to believe that he had phlebothrombosis, with a very large, patent foramen ovale). Whether or not one has to consider intrinsic liver disease and whether one can explain the icterus on the basis of a congestive liver, I do not know; I suppose it is possible. At these conferences I am frequently given a case of liver disease to discuss, and this probably will turn out to be one. I am going to say, however, that this man had massive gastrointestinal hemorrhage, perhaps from an ulcer. He had calcareous aortic stenosis, coronary insufficiency, old pulmonary infarction, auricular thrombi and many other conditions.

A Physician: Did the increase in clotting time occur after the administration of dicumarol or heparin?

Dr. Richardson: I do not know. I assumed that the heparin was not continued. It was used for immediate effect until the dicumarol took hold. I assume that that could account for the increase in clotting time and not the heparin, but I do not surely know.

I forgot about the x-ray films. Perhaps we should see them now.

Dr. James J. McCord: This is the chest film taken on admission. The left side of the heart is quite enlarged and probably represents an enlarged left ventricle. There is a plaque of sclerosis inside the aortic arch and a small amount of fluid in the costophrenic sinus. There is evidence of dilated vessels in the lung. This is the plain film of the abdomen, in which the liver does not appear to be enlarged; there are no dilated loops of bowel. We have two films of the stomach, and they do not show evidence of ulcer.

Dr. Richardson: I have no comment to make and no change in what I have said. I did not believe that there would be evidence of ulcer.

Dr. Alfred Kranes: Would Dr. Richardson consider the possibility of coronary thrombosis superimposed on an old syphilitic aortitis to account for the embolism to one arm, in addition to the possibility of mesenteric embolism to account for the abdominal pain?

Dr. Richardson: I agree. Very likely the emboli arose from a myocardial infarction. I thought of mesenteric arterial thrombosis, and I tried to say so but had too much language difficulty. However, I think that if the patient had had thrombosis of the mesenteric artery, he would not have been much better in two hours. On the contrary, he would have been much worse. Do you agree with that, Dr. Cope?

Dr. Oliver Cope: Yes; I think that is so.

Dr. Richardson: Also, mesenteric thrombosis results in a very high white-cell count. I have seen it go up as high as 75,000 or 80,000.

Clinical Diagnosis

Probable ventricular fibrillation.

Dr. Richardson's Diagnoses

Calcareous aortic stenosis.
Coronary insufficiency.
Pulmonary infarction (old).
Auricular thrombi.
Massive gastrointestinal hemorrhage (? ulcer).

Anatomical Diagnoses

Hypertrophy and dilatation of heart.
Syphilitic heart disease, with aortic insufficiency, minimal.
Syphilitic aortitis, minimal, inactive.
Chronic passive congestion.

Pathological Discussion

Dr. Mallory: Autopsy did not explain all the findings. The primary underlying disease was in the heart, which was very much hypertrophied, weighing 720 gm.; all the cavities and all four valve rings were uniformly dilated, and there was enough separation of the cusps of the aortic valve to make us believe that there had been syphilitic involvement. Seventy years is a very advanced age in which to see syphilitic involvement of the aortic valve. Patients with such a lesion ordinarily die at least a decade earlier than that.

Microscopical sections from the aorta showed some degree of vascularization of the media but almost no lymphocytic infiltration, which I think is consistent with a totally burned-out syphilis. There was no blood in the intestinal tract at the time of

autopsy, and nothing to explain the earlier episode of melena, which may have been due to dicumarol as Dr. Richardson suggested. The liver showed a moderate but not severe grade of passive congestion. There were no pulmonary infarcts. The coronary arteries were patent. The lungs were acutely congested and edematous, as in cases of acute heart failure.

One other interesting finding that we see very rarely at autopsy was marked dilatation of all the lacteals in the duodenum and jejunum with fat-containing chyle. There was also a considerable amount of fat residue in the stomach. In medicolegal cases in which death is instantaneous, it is not rare to see lacteals containing chyle. We see it here not more than once in several hundred autopsies, presumably because the digestive processes slow down and stop many hours before the patient dies. That is a physiologic phenomenon, however, with no pathologic significance.

There was one peculiar finding, which I cannot explain — a few small foci of active hematopoiesis in the liver and a few more in the spleen. The bone marrow showed disproportionate activity of the red-cell series but a total cellularity that was rather below normal than above. This suggests that the patient had a moderate degree of blood dyscrasia, which I am unable to diagnose. The spleen weighed only 190 gm., which is well within normal limits, and it is unlikely that this was a hemolytic anemia.

Dr. Kranes: Then no source was found for the embolus in the arm?

Dr. Mallory: No.

Dr. Richardson: According to you, the patient is still alive.

Dr. Mallory: He had a markedly hypertrophied and dilated heart.

Dr. Richardson: He probably died of ventricular fibrillation or something of that sort. Perhaps the quinidine dosage should have been increased, but perhaps those treating the patient were afraid to do so because of the embolus.

Dr. Mallory: The degree of aortic-valve involvement was minimal. I do not believe that one could blame the cardiac hypertrophy and failure on aortic insufficiency.

CASE 34142

Presentation of Case

A seventy-six-year-old widow entered the hospital because of inability to swallow.

The patient had been in excellent general health until about six months before admission, when she had an episode of abrupt syncope following a fall, with two similar episodes in the next few months; there were, however, no convulsions, and rapid recovery of consciousness followed each episode. One month before admission she noticed the abrupt onset of dysphagia followed by the inability to swallow anything but liquids. She reported the presence of a crampy, substernal pressure sensation, which was relieved by regurgitation of undigested food. In the week before entry the patient noticed some bright-red blood streaking in the regurgitated material, but there had been no previous bleeding. There was no radiation of pain and no abdominal or systemic symptoms. She had lost a great deal of weight in the three weeks before admission but did not know the exact amount. She denied chest pain, dyspnea, hemoptysis, ankle swelling, jaundice, melena or changed bowel habits.

Figure 1.

Physical examination revealed a well developed, poorly nourished woman with a moderate memory defect who was coughing frequently but was in no obvious distress. Examination of the chest and abdomen was negative.

The temperature was 99.6°F., the pulse 100, and the respirations 26. The blood pressure was 130 systolic, 75 diastolic.

Urinalysis revealed a + test for albumin and rare red cells and 10 white cells per high-power field in the sediment. The hemoglobin was 12.4 gm., and the white-cell count was 9000, with 86 per cent neutrophils. The serum protein was 5.7 gm. per 100 cc., the chloride 104 milliequiv. per liter, and the nonprotein nitrogen 22 mg. per 100 cc. The sedimentation rate was 23 mm. in one hour.

X-ray films of the chest revealed elevation of the right side of the diaphragm, with partial fixation and fluid in the right costophrenic angle. There were areas of haziness and mottled density throughout the entire right lung field, with an area suggesting infiltration in the first and second interspaces; the left lung field showed mottled areas of density. The left main bronchus was well seen, but the right was not visualized. A barium swallow demonstrated a smooth, fusiform narrowing in the esophagus for a distance of 5 cm. just below the carina (Fig. 1), but there was no evidence of shelf formation, destruction of the mucosa or ulceration. Passage of barium was delayed, but there was no true obstruction.

Bronchoscopy demonstrated a concentric constriction below the right middle-lobe orifice, but no biopsy was obtained. Esophagoscopy demonstrated an obstruction 19 cm. from the upper gum, which appeared diffuse and granular. The biopsy was reported as showing chronic inflammation. Cytologic examination of the sputum was reported as doubtful.

During the period of study the patient deteriorated rapidly. She developed anxious, gasping respirations and duskiness of the nail beds, ears and nose. Laminograms of the right lower-lobe bronchus showed an apparent area of narrowing about 1 cm. below the upper-lobe orifice. Later chest examination demonstrated dullness over the entire right side, with absent breath sounds over the upper third. Another examination of the sputum on the fourteenth day was negative for tubercle bacilli but positive for tumor cells. The patient went downhill progressively and died on the eighteenth hospital day.

Differential Diagnosis

Dr. Edward D. Churchill: Inasmuch as no statement is made to the contrary, I assume that there were no neurologic residua to the episodes of syncope. They sound like manifestations of cerebral arteriosclerosis or vascular insufficiency. We might inquire about the radiation of pain in the chest. Radiation to the back comes from certain mediastinal lesions.

Loss of weight, presumably, is determined by reduced dietary intake. Of course, a patient who cannot swallow anything is going to lose weight.

The sedimentation rate was 23 mm. in one hour. Is that a normal rate?

Dr. Marian W. Ropes: That is a definite increase in sedimentation rate.

Dr. Churchill: What I should like to know is whether that rate was normal for a woman seventy-six years of age who was losing a good deal of weight.

Dr. Ropes: The sedimentation rate should not be elevated because of weight loss.

Dr. Churchill: But you are not sure?

Dr. Ropes: No.

Dr. Churchill: I do not like the word "partial" fixation of the diaphragm. I consider fixation an absolute term. The diaphragm either was fixed or it was not fixed. Is there any further statement about that in the record?

Dr. Stanley M. Wyman: The diaphragm was fixed peripherally but moved centrally.

Dr. Churchill: Then part of the diaphragm was fixed. The qualifying adjective "partial" refers to diaphragm, not to fixation. Would you mind showing us the films now?

Dr. Wyman: The single film of the chest available shows the right leaf of the diaphragm to be elevated. It was fixed laterally and moved much less freely centrally than the left leaf did. The area of density described is best seen in the right lower-lung field; it also shows in the right upper-lung field, where there seems to be localized consolidation or density in the region behind the second rib. The areas of fine, linear density in the left lung field one might expect in a seventy-six-year-old woman. The heart is a little larger than normal, without characteristic configuration.

Dr. Churchill: Is there fluid in the right costophrenic angle?

Dr. Wyman: Yes; and possibly a small amount in the left.

Dr. Churchill: The left main bronchus was well seen, but the right was not visualized. Barium demonstrated narrowing in the esophagus.

Dr. Wyman: These spot films best demonstrate the area of narrowing of the esophagus, just below the carina. The narrowing appears to be distensible and to change in contour, suggesting that it is flexible. The left main bronchus is well seen on the spot films, but the right is not visualized beyond the bifurcation of the trachea. In this view a short segment of the right main bronchus is seen that seems to taper. I can see no evidence of ulceration of the esophageal mucosa and no shelf formation.

Dr. Churchill: What is shelf formation?

Dr. Wyman: It is the term used to describe, somewhat inaccurately, the margin of a tumor mass, which may represent intrinsic or extrinsic tumor pressing on the esophagus or growing in the wall. It is seen, unfortunately, in inflammatory conditions also and is not, per se, a sign of tumor.

Dr. Churchill: The passage of barium was delayed, but there was no true obstruction?

Dr. Wyman: That is correct.

Dr. Churchill: The films of the stomach show how easily barium filled the stomach.

Dr. Wyman: We have a satisfactory examination of the stomach and duodenum. The esophageal delay is apparent in the spot film taken in the upright position. The esophagus can be seen proximal to the narrowing. It is not dilated as in a true obstruction. The stomach itself shows no disease. The duodenal cap and proximal duodenal loop are normal except for a diverticulum. There

are a few areas of calcification in the region of the right kidney, which are probably renal calculi.

DR. CHURCHILL: Laminograms of the right lower-lobe bronchus were done. May we see them?

DR. WYMAN: This is the film that shows the lesion best, although it is not ideal. One can trace the left main bronchus quite readily and the right main bronchus for a short distance from the bifurcation. The upper-lobe bronchus is seen coming off and it appears of good contour. The lower lobe bronchus is poorly visualized and is definitely narrowed in a fusiform manner. I cannot make out a mass in this region. The pleural fluid has increased considerably since the first observation.

DR. CHURCHILL: Later on, dullness is described over the entire right side of the chest, with absent breath sounds in the upper third. The physical findings were therefore changing, and there was increased fluid in the chest.

DR. WYMAN: Yes.

DR. CHURCHILL: This woman was bronchoscoped, and it was observed that she had a concentric constriction of the right middle-lobe orifice. No biopsy was obtained at that time. Later, an esophagoscope was passed, and a biopsy obtained. The report of "doubtful" is of no help.

This history is obviously a trap. There are just enough findings in it that are atypical for carcinoma to make one reluctant to swing with the laboratory to a positive diagnosis of cancer. First of all, the x-ray peculiarities have been pointed out and, also, the negative findings on both bronchoscopy and esophagoscopy. If we are to resolve the problem by a diagnosis of tumor on the basis of the identification of tumor cells in the sputum, we must postulate a primary tumor in the bronchus, with secondary mediastinal involvement by metastatic disease. Cancer, primary in the esophagus, may involve the left primary bronchus. It does not involve the right primary bronchus below the level of the middle-lobe bronchus unless extraordinarily far advanced. The diagnosis of cancer of the esophagus has been made by bronchoscopy when the tumor was penetrating the left primary bronchus. But I doubt on anatomic grounds that the primary growth by direct invasion would pick off these two areas. One possibility, then, is primary bronchiogenic carcinoma in the right lung, with mediastinal extension or metastases producing secondary obstruction to the esophagus. Another is that this whole picture was caused by metastases from a primary focus elsewhere in the body. We have seen cancer of the cervix — a very small early carcinoma of the cervix — manifest itself by obstruction to the esophagus in just this area by spreading up through the retroperitoneal lymph nodes to the mediastinal lymph nodes. No mention is made of an extrathoracic focus of neoplasm in the case under discussion. I do not know whether or not complete physical examination included visualization of the cervix and precise examination of other likely areas of primary neoplasm in a woman of this age. We would like to see a statement that the breasts, for example, were not involved. We have to assume that the physical examination was complete and negative.

So far as differential diagnosis between neoplasm and inflammation is concerned, there is a great deal in favor of inflammation, particularly the nature of the lesion of the esophagus. It is described as a long, attenuated lesion, without obstruction. It is as though the esophagus were being gripped in a chronic, sclerosing, inflammatory lesion. What that could be is hard to say. We do know that tuberculosis produces such a lesion. We have had cases at these conferences in which tuberculosis of the mediastinum caused a similar picture. It is likely to occur in elderly persons. In favor of tuberculosis is the apical lesion pointed out by x-ray examination. The other lesions in the lung parenchyma could have been caused by esophageal regurgitation with food and mucus running down the windpipe and producing pneumonitis in this area of the lung. It would not account for the fluid in the pleural space unless there was an active pneumonia. There should also have been some signs of invasive infection from pneumonia.

Sputum examination was negative for tubercle bacilli but positive for tumor cells. On that evidence we must take the position that this lesion was not inflammatory but neoplastic. The statement that tumor cells have been demonstrated in the sputum is a definite one. There are cases in which the cytologic evidence can be taken as positive evidence. There are others in which we may have to put cytologic findings on a par with other clinical findings. Malignant cells were demonstrated in the sputum, so that the diagnosis must conform to that evidence and we must take the position that this woman had a cancer. All we can do is point out that there are many aspects of this case in which, in the absence of that finding, we would incline toward an inflammatory lesion — tuberculosis. Except for tuberculosis it is very difficult to picture an inflammatory lesion with a normal white-cell count and a normal temperature producing this type of process. The accumulation of fluid worries me a little, whatever diagnosis we accept. I wish we knew what it was — whether it had been aspirated, which would be another chance to demonstrate tumor cells, if it was a carcinoma.

With the evidence as presented, we can do no more than say that positive evidence of malignant cells, with the story and x-ray findings, allows no other tenable diagnosis than cancer. I expect it to be primary in the right bronchial tree, involving the esophagus by direct invasion and metastatic spread. In the absence of the positive findings of a malignant lesion, I would have leaned toward an inflammatory lesion, most likely tuberculosis.

A PHYSICIAN: How about the syncope?

DR. CHURCHILL: It is described as syncope following a fall. I suspect that the fall was caused by the syncope. A cerebral arteriosclerosis was manifested in the hospital by memory defect.

A PHYSICIAN: Could it have been tumor of the brain?

DR. CHURCHILL: Without localizing signs, I would not make a diagnosis of such a tumor.

DR. KING: These reports on tumor cells are checked by the head of the Vincent Laboratory, who has had much experience with this procedure, and when the report comes back positive I hate to throw it out. I think in this case the report came through very late in the course of study, but it did corroborate our opinion that the disease was neoplastic and not inflammatory. Where it had originated, we could not tell. The patient was too sick to go through many examinations to determine the source. She developed fluid quite rapidly just before death.

CLINICAL DIAGNOSIS

Carcinoma of esophagus.

DR. CHURCHILL'S DIAGNOSIS

Bronchiogenic carcinoma, primary in right lower lobe, with secondary involvement of esophagus.
Cerebral arteriosclerosis?

ANATOMICAL DIAGNOSES

Bronchiogenic carcinoma, right lower-lobe bronchus, with extension to esophagus and metastases to mediastinal lymph nodes, liver and omentum.
Thrombosis of pulmonary artery, right lower lobe.
Arteriosclerosis, generalized, severe.
Hydrothorax, bilateral.
Duodenal diverticulum.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: Autopsy showed extensive carcinoma, and the problem to be settled is where it was primary. The two largest masses of tumor were found in the right lower lobe and an annular mass that encircled the esophagus. There was a secondary, entirely separate lesion of the esophagus as well. The tumor in the esophagus had invaded and involved the serosa and muscularis but at no point the mucosa, and there was no point of ulceration, which would be extremely unusual in a primary cancer of that area. The right lower-lobe bronchus was completely surrounded by tumor, and there was widespread extension of the tumor through the lung via the lymphatic channels. The findings there were consistent with primary bronchiogenic carcinoma of the right lower-lobe bronchus. Although no point of ulceration in the bronchial mucosa could be demonstrated, the bronchus became rapidly and completely stenosed.

Histologic examination, which does not help us any further, disclosed a wildly undifferentiated tumor, and it is quite impossible to say whether it arose from squamous or glandular cells. A few of the cells were vacuolated and might suggest mucin production, but we were unable to prove that to our satisfaction. There were metastases in the mediastinal lymph nodes, in the mesentery and in the liver. We were not able to examine the brain, so that we cannot say whether it contained metastases. Our final diagnosis was bronchiogenic carcinoma, right lower-lobe bronchus, with secondary involvement of the esophagus.

DR. CARROLL C. MILLER: Did the X-ray Department believe that the haziness and the irregular areas represented lymphatic spread?

DR. WYMAN: The original interpretation was that the haziness in the right lung was suggestive of lymphatic metastases.

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SAVING THE NEWBORN INFANT

A COMMUNICATION published elsewhere in this issue of the *Journal* calls attention to a most progressive step that has been taken in behalf of the newborn infant. This step, another important undertaking of the American Academy of Pediatrics, is the establishment in every state of the union of committees to develop and improve facilities for the hospital care of newborn infants.

The need for this action was indicated by Dr. Stewart H. Clifford* in a paper read before the Massachusetts Medical Society in May, 1947, calling attention to the greatly increased demand for hospitalization of obstetric patients and the alarming increase in communicable diseases of the newborn. Dr. Clifford is chairman of the central committee on the fetus and newborn of the American Academy of Pediatrics.

These new committees wield no rubber stamps. They are out to produce results, both on their own initiative and in holding up the hands of public-health authorities. In Massachusetts the Department of Public Health has been preparing a new set of regulations for nursery construction and operation. The state committee will participate in such planning, and will co-operate in every other way with the Department.

As a useful guide to be followed voluntarily by hospitals until such time as these regulations may be put in force, Regulation 35 of Chapter II of the New York State Sanitary Code, enacted in January, 1948, is recommended for use, and is printed in the communication to which reference has been made. This regulation embodies the best known precautions that may be used for the control of diarrhea of the newborn infant.

*Clifford, S. H. Diarrhea of newborn. *New Eng. J. Med.* 237:969-976, 1947.

CANCER-DETECTION CLINICS

IN THE desire to do all possible in controlling cancer there have been evolved several types of cancer-detection clinics, and a great popular interest has been engendered in them. In fact any state that does not contain one or more of these clinics tends to be looked upon as decidedly backward in its cancer program. Forty of the states now have clinics of this type, and some four hundred of them exist altogether.

Both the American Medical Association and the American College of Surgeons have recognized the desirability of these clinics and have laid down certain principles for their establishment and operation.

The purpose of the clinics is essentially to examine healthy persons to determine whether or not they are harboring precancerous conditions, early cancer or other incipient pathologic processes. An analysis of the clinics was presented at the annual meeting of the New England Surgical Society on October 4, 1947, by Dr. Charles L. Larkin, of Waterbury, Connecticut, who pointed out a number of fallacies in the fundamental thesis of their operation.

To carry out annual examinations of the type proposed by some enthusiasts would require the entire time of every doctor in the United States, according to Dr. Larkin. The cost would be at least one and a quarter billion dollars a year. The clinics as operating at the present time defeat their very purpose in that prospective examinees are booked for months ahead, and hence delay is encouraged should any symptoms appear in the interim.

The popularity of these clinics, however, is so great that in all probability, since Massachusetts is one of the few states that does not have one, one or more will be organized by lay groups if the medical profession does not act.

There is no question that the most effective place for a cancer-detection examination is the office of the private physician. However, it is far from certain what types of diagnostic procedures are best suited to detect early cancer and what costly accessory services, such as x-ray and laboratory procedures, are warranted.

There has been proposed by the staff of the Palmer Memorial Hospital and recommended by the Committee on Cancer of the Massachusetts Medical Society and approved by the Council of the Society the establishment of a new type of cancer-detection clinic at the Palmer Memorial Hospital. This clinic would have as its primary purpose not the examination of a few hundred persons a year to determine whether or not they had cancer, which would be of little significance in the over-all problem, but rather would attempt to determine procedures in cancer diagnosis that would be of value to the practitioner and would so evaluate the laboratory and x-ray services as to enable those most useful to be selected and to avoid the expense of a wide range of laboratory and radiologic procedures.

It is important to keep in mind that all a cancer-detection clinic provides is an opportunity for a thorough physical examination with ancillary services. Properly organized, these clinics do not conflict with already existing tumor clinics or cancer clinics because the detection clinics are concerned primarily with healthy persons whereas the patients referred to the cancer clinic or tumor clinic already have developed a lesion.

A cancer-detection clinic of the type suggested for the Palmer Memorial Hospital might well not only be a very real asset to the practicing physician but also set a more realistic and practical pattern for such clinics throughout the country.

A STEP FORWARD

A MEDICAL rehabilitation clinic in Boston has been planned, and a petition requesting incorporation has been filed. The purposes of the proposed clinic are as follows:

> To maintain a charitable medical rehabilitation clinic or clinics for the benefit and treatment of convalescent patients . . . to assist in the restoration of such patients to gainful economic independence . . . to maintain facilities for the evaluation, restoration and improvement of the remaining physical abilities of persons crippled or handicapped as a result of war, disease, accident or other causes . . . referred to it by government and civilian hospitals, industrial and other clinics and by members of the medical profession . . . .[1]

This new type of medical clinic was originally conceived by one of our ablest and most respected statesmen, Mr. Bernard M. Baruch. He recognized the gap that existed in medical care between the time the patient left the hospital and the time he resumed normal routine productive activity. In 1944 he established The Baruch Committee on Physical Medicine,[2] which, working with a civilian scientific advisory committee and with representatives of the surgeons general of the armed forces, developed a plan based on the program of convalescent training and reconditioning treatment in military and naval hospitals, but also applicable to civilian communities. In 1946 the report on A Community Rehabilitation Service and Center[3] was published by the Baruch Committee on Physical Medicine. This stimulated in communities great interest toward the establishment of medical facilities or clinics that might specialize in the treatment of the seriously disabled convalescent patient.

New York University College of Medicine has already established a Department of Rehabilitation with Professor Howard A. Rusk as chairman. He will direct the project planned as part of the New York University–Bellevue Hospital Medical Center. The College of Physicians and Surgeons of Columbia University has placed Dr. Frank E. Stinchfield in charge of its recently affiliated Institute for Crippled

and Disabled. Toronto, Canada, has a state-operated rehabilitation center that appears to be functioning not only for medical treatment of convalescence but also for active vocational guidance and training. Cleveland and Milwaukee have had rehabilitation workshops operating successfully for a number of years. Bridgeport, San Francisco and Kansas City have, or are now establishing, rehabilitation centers. Although Boston has one medically supervised rehabilitation center operated for the benefit of the clients of one insurance company only,[4] it needs one open to the public.

The Council of the Massachusetts Medical Society passed a resolution on May 24, 1947, recognizing the need for a rehabilitation center in Boston. Pursuant to this resolution, on February 26, 1948, a petition requesting the incorporation of The Bay State Medical Rehabilitation Clinic was filed with the Department of Public Welfare. The authorities are urged to grant this petition, so that the Commonwealth may have an opportunity to provide for its physically handicapped citizens some of the newer concepts of medical rehabilitation. The Division of Vocational Rehabilitation of the Department of Education could utilize the services of this new nonprofit private charity. The charter provides for the training of personnel, many of whom will be qualified to staff similar centers in other communities. The disabled citizens of Massachusetts should have medically supervised rehabilitation services as good as or better than those of other states. There is no reason why this new type of medical charity should not be granted incorporation promptly.

Many permanently disabled citizens can be rehabilitated to gainful economic self-sufficiency. It takes courage to start a new charity at the present time. The Commonwealth will benefit by the establishment of such a clinic. The people of Boston need this medical service.

References

1. Agreement of Association of The Bay State Medical Rehabilitation Clinic on file with the Department of Public Welfare, Commonwealth of Massachusetts.
2. *Report on "A Community Rehabilitation Service and Center."* 24 pp. New York: The Baruch Committee on Physical Medicine, 1945. P. 5.
3. *Report on A Community Rehabilitation Service and Center.* 24 pp. New York: The Baruch Committee on Physical Medicine, 1946.
4. Aitken, A. P. Rehabilitation of employee injured in industry. *New Eng. J. Med.* 237:903-905, 1947.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

McOwen — William H. McOwen, M.D., of Newton Upper Falls, died on March 9. He was in his eighty-seventh year.

Dr. McOwen received his degree from Harvard Medical School in 1883. For sixty years he was a member of the staff of Newton Hospital.

Four daughters, two sons, seventeen grandchildren and two great-grandchildren survive.

Robinson — Leon J. Robinson, M.D., of Palmer, died on February 1. He was in his forty-second year.

Dr. Robinson received his degree from Boston University School of Medicine in 1934. He was a member of the staff of Monson State Hospital and was a fellow of the American Medical Association.

Two sisters survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

PROPER USE OF GAMMA GLOBULIN

The decision of the physician to use gamma globulin to prevent measles calls for the critical consideration of many factors. The indiscriminate use of the material on all children who have been exposed to measles is entirely unwarranted. Indications for various age groups may be summarized as follows: under six months prevention is unnecessary if the mother has had measles but is indicated if there is no history of measles in the mother; six months to three years (measles is most dangerous in this period) prevention is recommended; and over three years (measles is relatively mild with present available therapy) prevention is never justified, except in special circumstances such as sick or debilitated persons of any age or in children's institutions or hospital wards where it causes many cross infections. The use of gamma globulin for modification of measles in this or older age groups is justified.

Measles in a healthy child almost always confers lifelong immunity and causes at the most a loss of two weeks' play or school in the lower grades. Passive prevention at this age may mean that the person will later have measles — perhaps more severely as an adult — at a time when it can mean the loss of a semester's work in high school or college, or serious loss of employment.

The use of gamma globulin in other diseases, for which no evidence of efficacy has accumulated, is considered a waste of a very expensive product. Present stocks are derived almost entirely from fractionation of the large amounts of surplus plasma left over from the wartime Red Cross plasma program. This globulin should be conserved, since there is as yet no source of whole blood in view sufficiently large to supply future needs. If present supplies are exhausted, physicians will be obliged

to purchase the globulin, since the Department of Public Health has no funds for this purpose.

A circular giving more detailed information regarding the use of gamma globulin will be furnished on request to the Division of Biologic Laboratories, 375 South Street, Jamaica Plain 30, Massachusetts.

MISCELLANY

FEDERAL SECURITY AGENCY CHILDREN'S BUREAU

Dr. Samuel M. Wishik, formerly of the New York City Health Department, has been appointed to the Children's Bureau of the United States Federal Security Agency to direct the planning work connected with the Bureau's program of grants-in-aid to the States for maternal and child health and for crippled-children's services.

In announcing the appointment, Dr. Martha M. Eliot, associate chief of the Children's Bureau, said that more effective health services are needed for the thousands of babies born prematurely, and the children suffering with cerebral palsy, rheumatic fever, hearing defects, cleft palate and many other handicaps.

ATOMIC ENERGY COMMISSION CANCER RESEARCH

The Atomic Energy Commission, according to a Washington Report on the Medical Sciences, has released its plans for the expenditure of $5,000,000 that it received from Congress last fall for cancer research. Most important of its activities will be provision of free radioisotopes to qualified handlers in approved institutions; financial support of research projects in hospitals, clinics and universities; establishment of cancer-investigation facilities at four Commission-operated laboratories; and continued aid to the Committee on Atomic Casualties of the National Research Council. This committee is investigating long-term effects on survivors of the Nagasaki and Hiroshima bomb explosion.

AMERICAN PSYCHIATRIC ASSOCIATION

Dr. Daniel Blain, formerly chief of neuropsychiatric services for the Veterans Administration, has accepted the newly established position of medical director of the American Psychiatric Association. The position has been created to provide the full-time services of a physician who will act for the Association as an authorized source of information and advice.

As medical director, Dr. Blain will make his services available to the members, to affiliate societies and to public and private organizations interested in the field of psychiatry. He will serve also to effect liaison with the public on subjects related to the work of the Association and to the general interests of society.

For the present Dr. Blain may be addressed at Georgetown University Hospital, Washington, D. C., or at the executive office of the American Psychiatric Association, Room 924, 9 Rockefeller Plaza, New York City 20.

APPOINTMENT OF SOCIAL-SERVICE WORKER AT HARVARD SCHOOL OF PUBLIC HEALTH

As part of a new program to study the role of family life in the health of children, the Harvard School of Public Health recently announced the appointment of Miss Elizabeth P. Rice, at present clinical professor of the social aspects of medicine at Yale University School of Medicine and assistant professor of the social aspects of nursing at the Yale School of Nursing, as the first social-service worker to the faculty.

As assistant professor of medical social work in the Department of Maternal and Child Health, Miss Rice will begin a study of the preventive aspects of social work. Particular emphasis in the new program will be placed on the role of the family in preventing the development of undesirable social habits in children. Also, attention will be directed to discovering unfavorable social factors as they relate to the health of the family.

Miss Rice, a native of Boston, received the A.B. degree from Wellesley College and the A.M. from Simmons College. Among the positions that she has held in the field of medical social work are assistant director of the Social Service Department, Boston City Hospital, and director of social service, Boston Dispensary, the New Haven Hospital and the Grace–New Haven Community Hospital. She is the author of several publications on the part that medical social work plays in medicine and nursing.

PROGRESS IN DENTAL MEDICINE

The Division of Dental Health of the Massachusetts Department of Public Health has completed the first year of its existence. During this period six studies concerned with the prevention of dental caries were in operation, and water-fluorination programs were established in the Belchertown and Wrentham State schools, with the Fernald State School as a control.

At the Daniel Butler School in Belmont a project has been started with the use of indium nitrate as a substitute for the fluorine salts in topical applications. In Brockton a study was set up on the effect of fluorine incorporated in dentifrices, in Medford one on the use of fluorine in mouth washes, and in Quincy one on the incorporation of fluorine in prophylaxis pastes, to be used twice yearly on a group of children.

At the Harvard School of Dental Medicine the announcement has been made of the promotion of Dr. Reidar F. Sognnaes, an authority on dental decay, to an associate professorship of dental medicine.

CORRESPONDENCE

COMMITTEE ON FETUS AND NEWBORN INFANT

To the Editor: The following physicians have been appointed by Dr. James M. Baty, state chairman of the American Academy of Pediatrics, to serve as a Massachusetts Committee on the Fetus and Newborn Infant: W. Bradford Adams, Springfield, Fred H. Allen, Holyoke, Joseph Garland, Boston, Paul J. Jakmauh, South Boston, Robert T. Moulton, Salem, Alfred S. O'Connor, Worcester, Herman Petterson, Boston, Clement A. Smith, Boston, Stuart F. Stevenson, Boston, and Alfred Weller, Arlington Heights. It is felt that readers of the *Journal* should be informed about the existence and function of this committee.

The American Academy of Pediatrics is setting up, in all the states, committees similar to this one, with the purpose of developing and improving facilities for the hospital care of newborn infants — full term and premature. These committees will act in co-operation with the state and local public-health authorities, as representatives of the practice of pediatrics as it touches related interests in this field. Although many of the problems to be attacked will not be those of infectious diseases in the newborn period, the prevalence of sporadic epidemics of diarrheal disease in newborn nurseries will obviously turn a considerable part of the committee's attention to that special subject.

Dr. Stewart H. Clifford, chairman of the Academy's national committee in this field, has called attention to the recently approved New York State Sanitary Code bearing upon diarrhea of the newborn. Dr. Clifford and members of the committee believe that the New York statement is so admirably succinct and complete that it is transmitted as deserving publication. It has obviously no legal status in Massachusetts but covers the problem so well that it might be highly useful to any hospital or physician faced with the prevention or management of an epidemic and is offered only with this purpose. The code is as follows:

CHAPTER II

Regulation 35. Precautions to be observed for the control of diarrhea of the newborn. It shall be the duty of administrators of general hospitals or child caring institutions, proprietors of maternity hospitals or maternity

homes, and physicians and nurses responsible for the care of normal newborn and premature infants in general hospitals or child caring institutions, or maternity hospitals or maternity homes, to take all reasonable precautions to prevent the introduction and spread of diarrhea of the newborn, including the following:

a. Formulae and other fluids offered to newborn infants in hospitals or child caring institutions, or in maternity hospitals or maternity homes shall be poured into individual feeding bottles at the time of preparation, and a nipple shall be attached to each bottle and covered with a cap. The entire product shall then be subjected to terminal heating by steam under pressure of not less than 15 pounds (121° Centigrade or 250° Fahrenheit) for not less than 5 minutes, or at a pressure of not less than 6 pounds (110°C. or 230°F.) for not less than 10 minutes, or by flowing steam at a temperature of not less than 100°C. (212°F.) for not less than 30 minutes. The temperature of the formula or fluid, as determined by periodic examination, shall be not less than 93°C. (200°F.) at the end of the heating process. The nipple cap shall remain on the bottle until the time of feeding. If fruit juices, or formulae containing lactic acid, meats, or cereals are given to newborn infants, they may be offered without such terminal heating, but shall be prepared with and stored in pre-sterilized equipment.

b. Normal newborn and premature infants born in a hospital or maternity hospital or maternity home shall not be kept in the same nursery, room or ward with sick infants or older children. Nurses giving care to infected patients shall not come in contact with infants in the normal newborn or premature infant nurseries. No infant born outside the hospital or maternity hospital or maternity home shall be admitted to the nursery for well infants, except after isolation for a period of one week. An infant born to a mother who has diarrheal or respiratory illness shall not be admitted to the nurseries for normal newborn or premature infants.

c. An infant suspected of having diarrhea of the newborn shall be promptly removed from the normal newborn or premature infant nurseries, and kept under isolation precautions. If, after observation, diarrhea of the newborn is found to exist, such infant shall then be transferred to an isolation nursery.

d. Individual equipment shall be provided for each infant except for the weighing scales, which shall be freshly covered for each infant. Common bathing and dressing tables are prohibited. The use of racks, carriers, or bassinet stands for holding or transporting more than one infant at a time is prohibited. Physicians and nurses shall wash their hands under running water before and after coming in contact with any infant.

e. Nursing care shall be given to each infant at the bedside. Space shall be adequate to give such care, provided that the total nursery floor space shall average not less than 24 square feet per infant, or the infants shall be placed in individual cubicles.

f. No room used as a nursery shall house more than 12 infants, nor shall such a room intercommunicate with other rooms used as nurseries. There shall be running hot and cold water for handwashing in each room used as a nursery, with the flow of water controlled by elbow, knee or foot valves. No nurse shall give care to more than 12 infants and their equipment.

Enacted January 16, 1948, to be effective January 1, 1949, except that the enforcement of either or both subdivisions "e" and "f" may be deferred for an individual institution for a period not later than January 1, 1951 by the State Commissioner of Health upon request of such institution.

The Massachusetts Committee on the Fetus and Newborn Infant, or its individual members, will welcome any opportunity to assist in planning for nursery construction or in giving informal advice regarding any problems concerning the health of newborn infants in the Commonwealth.

CLEMENT A. SMITH, M.D., *Chairman*

Boston

BOOK REVIEW

Diseases of Children. Edited by Donald Paterson, M.D. (Edin.), F.R.C.P., and Alan Moncrieff, M.D. (Lond.), F.R.C.P. Volume I, with contributions by twenty-nine authors. Fourth edition. 8°, cloth, 771 pp., with 154 illustrations. Baltimore: Williams and Wilkins Company, 1947. $9.00.

This first volume of a standard treatise, first published in 1913 in a single volume, is the joint work of twenty-nine English specialists in their particular fields. The third edition was issued in 1934, and a new edition planned before the outbreak of World War II had to be abandoned because of hostilities and consequent difficulties. This fourth edition has been expanded into two volumes, and the text and illustrations thoroughly revised to bring them up to date. Sections have been added on the surgical aspects of congenital deformities, growth and development; the use of drugs in infancy and childhood, including the sulfonamides and penicillin; clinical pathology; acid-base regulation; anesthetics in the surgery of childhood; subdural hematoma in infancy; the treatment of megacolon; abdominal pain; surgery of the lung; treatment of pneumonia; diagnosis and treatment of collapse of the lung; and much new material on tuberculosis. The volume is divided into two parts, general considerations and diseases of children, including diseases and injuries of the newborn, diseases of nutrition, metabolism, the ductless glands, the digestive tract, the respiratory system, tuberculosis and allergy. Selected references are appended to each chapter. A good index concludes the volume. The book is well published. It is recommended for all medical libraries and should prove valuable to all physicians interested in pediatrics.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Approaches to Tumor Chemotherapy: A symposium of papers and discussions on various aspects of tumor chemotherapy, developed from the summer meetings of the Section on Chemistry (C) of the American Association for the Advancement of Science at Gibson Island, Maryland, 1945–1946. Edited by Forest Ray Moulton. 4°, cloth, 442 pp., illustrated. Washington: The Association, 1947. $7.75.

Twenty-six main articles make up this special volume. Ninety-three specialists took part in the meetings in 1945 and 1946, and the main papers are included in this volume. The first part is a general review of cancer therapy. The second presents a series of papers on special methodology, the third, nutritional factors, the fourth, bacterial products, the fifth, nitrogen mustards, and the sixth, various clinical aspects. This series of papers reflects the current knowledge on the subject. The volume is well published in every way. It is recommended for all medical libraries, and should prove valuable to all physicians interested in tumors.

Entwicklungsgeschichte des Krankheitsbegriffes. By Dr. Emanuel Berghoff. Second edition. 8°, cloth, 201 pp. Wien, Verlag Wilhelm Maudrich, 1947. $5.00. *Wiener Beiträge zur Geschichte der Medizin.* Vol. I. Distributed in the United States by Grune and Stratton, New York.

This monograph on the historical development of the ideas of disease discusses in order the significance of pre-Hippocratic ideas and the early theories of disease, Hippocrates and his school, Galen and the Middle Ages, the Renaissance and the seventeenth century, followed by chapters on animism and neuropathology, mesmerism and the Romantic school, the period of the end of the eighteenth and the beginning of the nineteenth centuries, the Vienna School, and cellular pathology and the bacteriologic era, serology and constitutional pathology. The work concludes with a chapter on the significance of social medicine in relation to disease ideas. The volume is concluded with a short list of references and an author index. An index of subjects would be appreciated in

a succeeding edition. The text is well arranged and well written. The type and paper are good, and the printing is well done. The publication is up to the standard of prewar days. The monograph is recommended for all medical-history collections.

How Life is Handed On. By Cyril Bibby, M.A., M.Sc., F.L.S., senior lecturer, College of St. Mark and St. John, London. 8°, cloth, 159 pp., with 62 illustrations. New York: Emerson Books, Incorporated, 1947. $2.00.

This small book is intended for the use of children and young adolescents. The text is written in an easy style brought down to the educational level of the intended readers. The descriptions of the beginnings of life in animals and man are presented in a frank manner. There are additional chapters on the relation of the sexes, family life and adolescence, as well as one on the declining birth rate. The appendixes contain a list of simple biologic experiments, books for further study and a glossary of terms used in the text. There is an index of plant and animal names and one of subjects. The author does not set any minimum limit on the age of children for which the book is intended; therefore, it would be advisable for parents to pass on the book before giving it to their children. The printing, type and paper are good, and the price is reasonable.

Successful Dental Practice: Patient relations-patient education-treatment planning-business principles. By J. Lewis Blass, Ph.G., D.D.S., associate professor of periodontia, lecturer on practice management and lecturer on dental therapeutics, New York University College of Dentistry; and Irvin Tulkin, D.D.S. 8°, cloth, 221 pp., with 42 illustrations, including 1 color plate. Philadelphia: J. B. Lippincott Company, 1947. $6.00.

The authors write in detail on the management of patients, office management, fees, insurance, legal matters and other problems that effect the business of a dental practice. The text is concluded with an atlas for patient education. A good index completes the volume. Valuable suggestions are presented for the improvement of the business side of practice, some of which could be of value to physicians, especially those relating to patient management. The volume is well published.

Practical X-ray Treatment. By Arthur W. Erskine, M.D. Third edition, revised and enlarged. 8°, cloth, 155 pp., with 22 illustrations. Saint Paul: Bruce Publishing Company, 1947. $4.50.

The first edition of this manual was published in 1931, and the second in 1936, and this revision of 1947 seeks to correct the mistakes made in the preceding editions. The text is devoted to the methods used by the author in the treatment of skin diseases; infections and inflammations; nonmalignant conditions, such as hyperthyroidism, hypertrophy of the tonsils, scrofula and fibroid tumors; and cancer and malignant conditions. The first eight chapters deal with technic, dosage and effects on tissue. The chapter on scattering and distribution is illustrated with fourteen tables showing the back-scatter and distribution of x-rays of various degrees of quality under various physical conditions. The volume is well published in every way and should prove useful to physicians interested in the subject.

Osteophthisis Pelvis et Femorum: Zugleich ein Beitrag zur Frage der spontanen Rückbildung maligner Tumorem. By Dr. Gottfried Hartmann, Assistent des pathol. anat. Institutes der Universität Wien. 8°, cloth, 183 pp., with 19 illustrations. Wien: Verlag Maudrich, 1947. $5.00. Distributed in the United States by Grune and Stratton, New York. *Wiener Beiträge zur Pathologie und pathologische Anatomie.* Vol. I.

This monograph on tuberculosis of the pelvis and femora is based on a complete study, clinical, roentgenologic, pathologic and histologic, of a fatal case, in which both hips were involved. The patient was studied for a period of ten years. The histologic study of all tissues of the body after autopsy is comprehensive and is considered in the light of the question of spontaneous involution of malignant tumors. The text is divided into six parts: a short prologue, followed by the case history; a critical study of the histologic materials, including an interpretation of the findings; the etiology and pathogenesis of the condition and its problems; and a summary. The text concludes with a list of references. An index would be appreciated. The publishing is well done in every way. The histologic plates are excellent. The monograph should be in all large medical libraries.

La Médecine au Etats-Unis de 1940 à 1946. By Dr. Stanislaus Lasalle, en collaboration avec le Dr. A. Gottschalk. 8°, paper, 333 pp. Paris: Editions Hippocrate, 1946. 270 francs.

This volume consists of abstracts of the principal articles published in American medical periodicals during the period 1940–1946. Eighty-three different journals were consulted, and the coverage is good. The emphasis is on therapeutics and clinical medicine. The subjects of gynecology, obstetrics, pediatrics, surgery and experimental medicine are also included. The abstract is well done, and the book should prove valuable to French-speaking physicians.

Introduccion al Estudio de la Plasmoterapia. By Jose M. Massons, de la Sección de farmacologia del Instituto de Investigaciones Medicas de la Universidad de Barcelona. Prologo de Francisco Garcia-Valdecasas, Catedrático de farmacologia de la Facultad de Barcelona. 12°, paper, 276 pp., with 15 illustrations. Barcelona: Editorial Miguel Servet, 1947.

This valuable monograph on the use of blood plasma is essentially a review of the world's literature through the year 1945. The author, after a chapter on history, discusses in order physiopathology, hypoproteinemia and protidopenia, human and animal plasma and colloidal solutions, the indications of the use of plasma, the technic of its administration and the complications. The text is well organized and well written. The type and paper are excellent. Good indexes of authors and subjects conclude the volume. The monograph should be in all large medical libraries and should prove valuable to all persons interested in the subject.

Headache. By Louis G. Moench, M.D., assistant clinical professor, University of Utah School of Medicine, and internist, Salt Lake Clinic, Salt Lake City. 8°, cloth, 207 pp., with 58 illustrations. Chicago: Year Book Publishers, Incorporated, 1947. $3.50.

The researches of recent years have advanced greatly the knowledge of the troublesome symptom of headache. Dr. Moench has brought together in one volume for ready reference the latest ideas on the subject. He classifies the material according to the origin of the symptom: pathological anatomy and physiology, followed by headache from intracranial disease; spinal puncture and ventriculography; cranial-nerve neuralgias; headaches of ocular and nasal origin, from disease in the neck and from systemic disorders; histamine headaches; migraine; and headaches of emotional origin. A list of references is appended to each chapter, and a good index concludes the volume. The material is well organized. The printing is well done with a good type on good paper. The book is recommended for all medical libraries and should prove useful to the general practitioner, for whom it is written.

Neutron Effects on Animals. By the staff of the Biochemical Research Foundation. Dr. Ellice McDonald, director, Newark, Delaware. 8°, cloth, 198 pp. Baltimore: Williams and Wilkins Company, 1947. $3.00.

The cyclotron employed in these researches was specially constructed for biochemical and biologic study. During an investigation on the blood for the Manhattan District it ran continuously for more than a year without missing a day. For the past eight years the staff of the Foundation has been studying the forces and material produced by the machine. The twenty papers presented in this volume represent the preliminary studies on the effects of neutrons on body tissues and fluids of the lower animals. The volume is well published in every way, and its price is reasonable. This is a book in a new field and is recommended for all medical libraries.

Morphologic Hematology. Special issue No. 1 of *Blood, the Journal of Hematology.* William Dameshek, M.D., editor-in-chief. 4°, cloth, 200 pp. New York: Grune and Stratton, 1947. $4.75.

In this symposium twenty-six recognized authorities have combined in a discussion of the physiologic and pathologic morphology of the blood in man and in animals. The volume is well published in every way and should be in all medical libraries.

Training in Clinical Psychology. Transactions of the first conference, March 27, 28, 1947, New York City. 8°, paper, 88 pp. New York: Josiah Macy, Jr., Foundation. $1.50.

This small volume presents the various papers read at the conference of specialists held in New York in 1947. The discussions centered on the problems of training in clinical psychology and psychoanalysis. The type, paper and printing are good, but the ring type of binding is not suitable for permanent preservation of valuable material. However, the volume should be in all medical libraries.

Gifford's Textbook of Ophthalmology. By Francis H. Adler, M.D., professor of ophthalmology, University of Pennsylvania School of Medicine. Fourth edition. 8°, cloth, 512 pp., with 310 illustrations. Philadelphia: W. B. Saunders Company, 1947. $6.00.

This standard textbook has been revised in the light of the original concept of Dr. Gifford. The book is intended primarily for medical students and general practitioners, with emphasis on conditions that they may safely treat themselves. The technics of refraction and operations have been condensed considerably, and surgical procedures have been given a separate chapter. Special emphasis has been placed upon the relation of the eye to general medical and neurologic conditions. The references appended to each chapter have been confined to those in the English language. A good index concludes the volume. The text is well organized, and the publishing well done in every way. The book should prove useful to the general practitioner.

Pharmacology, Therapeutics and Prescription Writing: For students and practitioners. By Walter Arthur Bastedo, Ph.G., Ph.M. (Hon.), M.D., Sc.D. (Hon.), consulting physician, St. Luke's Hospital, New York, St. Vincent's Hospital, Staten Island and the Staten Island Hospital. Fifth edition. 8°, cloth, 840 pp., with 82 illustrations. Philadelphia: W. B. Saunders Company, 1947. $8.50.

This new edition of a standard reference work first published in 1913 has been completely rewritten. This has been made necessary by the therapeutic advances since the printing of the previous edition in 1937. Parenteral administration is given due consideration. Material has been added on the amino acids, blood fractions, coagulants and anticoagulants, heparin, dicumarol, curare, snake venoms, folic acid, rutin, thiouracil, sulfonamides, penicillin, streptomycin, demerol, metopon, the cardiac glycosides, the antimalarials, the mercury diuretics and the BAL treatment of poisoning by arsenic, gold and other substances. Details of the modern treatment of shock and of anemias, and syphilis are given. Carbon monoxide, carbon disulfide, the cyanides and lead are discussed, not as remedies but as serious poisons. A comprehensive index concludes the volume. The book is well published in every way, and a light paper is used, making a light volume for its size. It is recommended as a reference work for all medical libraries and for physicians.

Edinburgh Post-Graduate Lectures in Medicine. Volume III. 8°, cloth, 587 pp. Edinburgh: Oliver and Boyd, 1946. 15 sh.

This is the third of a series of volumes presenting in inexpensive editions the postgraduate lectures delivered in the Royal Infirmary of Edinburgh. This series comprises thirty lectures delivered during the season 1942–1943 by specialists and covers the whole field of medicine, including surgery. The volume is well published and should be in all medical libraries. It is an outstanding example of this type of publication.

Fundamentals of Immunology. By William C. Boyd, M.D., associate professor of biochemistry, Boston University School of Medicine. Second edition. 8°, cloth, 503 pp., with 50 illustrations and 66 tables. New York: Interscience Publishers, Incorporated, 1947. $6.00.

This textbook has been written primarily for students and research workers. First published in 1943, the book has been completely revised within the scope of its objective of presenting basic facts and not exhaustive discussions. Each chapter is documented with a list of references. The material is well organized, and the book is well published in every way and printed on a soft paper pleasing to the eye. It is an ideal textbook.

Developmental Diagnosis: Normal and abnormal child development: clinical methods and pediatric complications. By Arnold Gesell, M.D., and Catherine S. Amatruda, M.D. Second edition, revised and enlarged. 8°, cloth, 496 pp., with 21 illustrations. New York: Paul B. Hoeber, Incorporated, 1947. $7.50.

Dr. Gesell has thoroughly revised this new edition of his work, which was first published in 1941. A number of additional case studies have been incorporated in the text. They include diagnostic problems involved in amentia, convulsive disorders, cerebral injuries, blindness, deafness, infantile aphasias, congenital anomalies and prematurity. Material has been added on prenatal rubella, the Rh factor, retrolental fibroplasia and electroencephalography, as well as sections on behavior growth and hygiene of the fetal infant and on the physician's role in the problem of child adoption. The literature has been brought up to date. A good index completes the volume. The book is well published in every way. It is recommended for all medical libraries and should prove valuable to all physicians dealing with young children.

Handbook of Diagnosis and Treatment of Venereal Diseases. By A. E. W. McLachlan, M.D., Ch.B. (Edin.), D.P.H., F.R.S. (Edin.), consultant in venereal diseases, City and County of Bristol, lecturer in venereal diseases, University of Bristol, and honorary consultant in venereal diseases, Bristol General Hospital. Third edition. 12°, cloth, 375 pp., with 160 illustrations, 20 in color. Baltimore: Williams and Wilkins Company, 1947. $5.00.

The third edition of this British handbook has been revised to include the knowledge gained of the value of penicillin therapy. The soundness of the text is evidenced by the need of three editions in four years. The book reflects the best British opinions and experience. Manufactured in Great Britain, it is well printed with a good, large, legible type. Primarily intended for undergraduate and postgraduate students, it should prove useful to the general practitioner.

Fundamentals of Psychiatry. By Edward A. Strecker, M.D., Sc.D., LL.D., Litt.D., professor of psychiatry and chairman of the department, Undergraduate and Graduate School of Medicine, University of Pennsylvania, psychiatrist to the Pennsylvania, Philadelphia and Germantown hospitals, consultant and chief-in-service, Institute of Pennsylvania Hospital, and consultant to the Surgeon General, United States Navy. Fourth edition. 12°, cloth, 325 pp., with 21 illustrations. Philadelphia: J. B. Lippincott Company, 1947. $4.00.

This manual first published in 1942 has been thoroughly revised in this fourth edition. Much material has been added including a chapter on psychosomatic psychiatry. Two suggested nomenclatures have been included in the text. The soundness of the compend is evidenced by the demand for four editions since the publication of the first in 1942.

Practical Clinical Psychiatry. By Edward A. Strecker, A.M., M.D., Sc.D., Litt.D., LL.D., professor of psychiatry, University of Pennsylvania; Franklin G. Ebaugh, A.B., M.D., professor of psychiatry, University of Colorado School of Medicine, and director, Colorado Psychopathic Hospital; and Jack R. Ewalt, M.D., professor of neuropsychiatry and director, Galveston State Psychopathic Hospital, University of Texas Medical Branch. Section on *Psychopathologic*

Problems of Childhood. By Leo Kanner, M.D., associate professor of psychiatry, Johns Hopkins University School of Medicine. Sixth edition. 8°, cloth, 476 pp., with 35 illustrations and 12 tables. Philadelphia: Blakiston Company, 1947. $5.00.

This authoritative textbook, first published in 1925 and last revised in 1940, has again been revised in the light of the extensive knowledge of psychiatry gained during the years of World War II. This edition includes both the military and standard nomenclatures. An extensive bibliography is appended to each main section, and a good index concludes the volume. The book is well published in every way. It is recommended for all medical and mental libraries and to all physicians interested in psychiatry.

Public Health Law. By James A. Tobey, Dr. P.H., LL.D. Third edition. 419 pp. New York: Commonwealth Fund, 1947. $4.50.

Much material has been added to this new edition of a standard reference monograph. Approximately two hundred and fifty new decisions of courts of last resort on various aspects of public-health law have been referred to or abstracted; numerous alterations in governmental organization and administration have been noted, and important legislative trends have been reported. The text is well printed with a good legible type on soft, light paper. A general index and one of cases conclude the volume. The book is recommended for all medical, public-health and law libraries and should prove valuable to public-health officers and lawyers.

Communicable Diseases. By Franklin H. Top, M.D., M.P.H., medical director, Herman Kiefer Hospital, clinical professor of preventive medicine and public health, Wayne University College of Medicine, and extramural lecturer on infectious diseases and epidemiology, School of Public Health, University of Michigan. Second edition. 8°, cloth, 992 pp., with 95 illustrations and 13 color plates. St. Louis: C. V. Mosby Company, 1947. $8.50.

Dr. Top and his collaborators have revised all chapters of this standard work first published in 1941. Fourteen new chapters have been added on various diseases, and the number of collaborators has been increased to twenty. The chapters on influenza, malaria and rickettsial diseases has been completely rewritten. Many illustrations in black and white and in color have been added. A bibliography is appended to each chapter. The appendixes present morbidity tables and a glossary of medical words. A good index concludes the volume. The book is recommended for all medical libraries and to all physicians interested in communicable diseases.

A Textbook of Clinical Neurology: With an introduction to the history of neurology. By Israel S. Wechsler, M.D., clinical professor of neurology, Columbia University, neurologist, Mount Sinai Hospital, and consulting neurologist, Montefiore Hospital and Rockland State Hospital, New York. Sixth edition. 8°, cloth, 829 pp., with 162 illustrations. Philadelphia: W. B. Saunders Company, 1947. $8.50.

The first edition of this standard textbook was published in 1927, and the previous revision was made in 1943. This sixth edition has been revised to bring the text up to date. Material has been added, and the chapter on psychometric tests has been completely rewritten and its name changed to Psychologic Diagnosis. The list of references attached to each chapter has been revised by the inclusion of new titles and the deletion of obsolete references. A comprehensive index concludes the volume. The book is well published in every way in the characteristic style of the publisher. It is recommended for all medical libraries and to all persons interested in neurology.

The Rotunda Hospital, 1745–1945. By O'Donel T. D. Browne, M.B., M.A., M.A.O. (Univ. Dublin); F.R.C.P. (I); F.R.C.O.G. King's professor of midwifery, Trinity College, Dublin; gynecologist, Sir Patrick Dun's, Monkstown, and Stewarts' Hospitals, Dublin. 4°, cloth, 296 pp., with 44 plates and a chart. Baltimore: Williams and Wilkins Company, 1947. $11.00.

In this volume is portrayed the history of the Rotunda Hospital of Dublin, Ireland. The book is divided into six parts. The first two are devoted to a chronologic history of this famous obstetric hospital and the Dublin School of Midwifery. The succeeding chapters discuss the struggle against puerperal fever, operative midwifery, anesthesia, gynecology and eclampsia. In the section on puerperal fever the part Oliver Wendell Holmes of Boston played in the prevention of this disease is fairly and impartially discussed. The volume is well published in every way. It is printed with a good large type on soft paper. The book should be in all medical-history collections.

Endocrinology of Neoplastic Diseases: A symposium by eighteen authors. 8°, cloth, 392 pp. New York: Oxford University Press, 1947. $11.00.

This symposium, originally published in *Surgery* in 1944, has been revised and brought up to date as of 1946. The various papers discuss the endocrinologic aspects of tumors of the pituitary body, ovary, uterus, breast, prostate, testicle, adrenal glands, thyroid and parathyroid glands, pineal gland and the pancreas and present the latest information on the various topics. A long bibliography is appended to each chapter. The printing is well done with a good type but on a heavy, filled paper not essential for this type of book. The price seems excessive for the volume. The work is recommended as a reference text for medical libraries and should prove valuable to physicians interested in the subject.

Clinical Pediatrics. By I. Newton Kugelmass, M.D., Ph.D., Sc.D., attending pediatrician, Downtown Hospital, Pan-American Clinic, Lynn Memorial Hospital, Monmouth Memorial Hospital and Muhlenberg Hospital, New Jersey. Second edition. 8°, cloth, 409 pp. New York: Oxford University Press, 1947. $4.00.

The purpose of this epitome is to emphasize the determining features of pediatric problems as a basis for more detailed study of the individual child in health and disease. The material is arranged in an outline manner and divided into eighteen parts, based on an anatomic classification. The volume is well printed and should prove useful to physicians interested in pediatrics, and should be valuable in differential diagnosis.

Essentials of Pharmacology. By Frances K. Oldham, M.Sc., Ph.D., research associate in pharmacology, University of Chicago; F. E. Kelsey, Ph.D., associate professor of pharmacology, University of Chicago; and E. M. K. Geiling, Ph.D., M.D., Frank P. Hixon Distinguished Service Professor and chairman of the Department of Pharmacology, University of Chicago. 8°, cloth, 440 pp. Philadelphia: J. B. Lippincott Company, 1947. $5.00.

This manual is intended as an introductory text in pharmacology in which the general principles of the subject are stressed. The text is divided into three parts: general principles, functional drugs and chemotherapeutic agents. To each chapter is appended a selected list of references for further reading. A good index concludes the volume. The text, printed on a good soft paper, should prove useful to students and others desiring a good compendium of the subject.

Endogenous Endocrinology: Including the causal cure of cancer, compendium. By Dr. Jules Samuels. 8°, cloth, 539 pp., with 30 illustrations. Amsterdam, Holland: Holdert and Company, 1947. $10.00.

The author is contemplating the publication of a large five-volume treatise on endogenous endocrinology, and is issuing this volume as a preliminary compendium to his treatise. He outlines his theory of hypophyseal dysfunction and of its relation to various diseases. He believes that restoration of the balance of the pituitary gland may arrest tumor growth. He claims that after his method of treatment a number of patients have survived for five to seven years and have continued to enjoy good health. The first part of the book discusses the subject in general and the use of the short-wave current in treatment. The second part considers the various diseases susceptible to treatment, with a long section on proliferation diseases, including cancer. The book is well printed on good paper but is unduly bulky for its size. All physicians interested in cancer should have access to this volume.

NOTICES

ANNOUNCEMENTS

Dr. Varaztad H. Kazanjian announces that Dr. Aram Roopenian and Dr. Alfred Joseph are now associated with him in the practice of plastic and maxillo-facial surgery at 475 Commonwealth Avenue, Boston.

Dr. Max H. Rodman announces the removal of his office to 175 Maple Street, Malden.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston
Lecture Hall, 9–10 a.m.

MEDICAL CONFERENCE PROGRAM

Friday, April 2 — The Etiology and Treatment of Motion Sickness. Dr. Robert S. Schwab.

Wednesday, April 7 — Pitfalls in Diagnosis and Disposition of Chest Disease. Dr. Lowrey F. Davenport.

Friday, April 9 — The Problem of Local Health Units in Massachusetts. Dr. Hugh R. Leavell.

Wednesday, April 14 — Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon.

Friday, April 16 — Certain Renal Complications in Diabetes. Dr. George V. Mann.

Wednesday, April 21 — Recent Advances in Anesthesia. Dr. Philip S. Marcus.

Friday, April 23 — Relief of Pain by Neurosurgical Procedures. Dr. William H. Sweet.

Wednesday, April 28 — Newer Concepts of Muscle Contraction. Dr. Gerhard Schmidt.

Friday, April 30 — Medical Experiences in Germany (March, 1948). Dr. Alexander Marble.

On Tuesday and Thursday mornings from 9 to 10 Dr. S. J. Thannhauser will give medical clinics on hospital cases. On the second and fourth Friday afternoons of each month therapeutic conferences will be held from 2 to 4 with round-table discussion, Dr. R. P. McCombs, moderator; Dr. Merrill Sosman will conduct x-ray conferences from 4 to 6. On Saturday mornings from 9 to 10 clinics will be given by Dr. William Dameshek. Medical rounds are conducted each weekday except Saturday by members of the staff from 12 to 1.

All exercises are open to the medical profession.

BERKSHIRE DISTRICT MEDICAL SOCIETY

The annual meeting of the Berkshire District Medical Society will be held at the Williams Inn, Williamstown, on April 15, at 7 p.m.

There will be election of officers. Brief talks will be given by Dr. John F. Conlin, director of medical information and education, Massachusetts Medical Society, and by Dr. Charles G. Hayden, medical director, Massachusetts Medical Service and Massachusetts Hospital Service.

CHRISTIAN MEDICAL SOCIETY

The second annual convention of the Christian Medical Society will be held in Chicago on June 25 and 26. Meetings are to be held in the Illini Building, 715 South Wood Street, on the campus of the University of Illinois. Advance registration and all correspondence should be addressed to the Christian Medical Society, 64 West Randolph, Chicago 1, Illinois.

AMERICAN OPHTHALMOLOGICAL SOCIETY

The annual meeting of the American Ophthalmological Society will be held in Hot Springs, Virginia, from May 17 to 19 (secretary, W. S. Atkinson, M.D., 129 Clinton Street, Watertown, New York).

AMERICAN OTOLOGICAL SOCIETY

The annual meeting of the American Otological Society will be held at "The Homestead," Hot Springs, Virginia, on April 12 and 13.

AMERICAN PSYCHIATRIC ASSOCIATION

The annual meeting of the American Psychiatric Association will be held in Portland, Oregon, from May 9 to 14 (secretary, Leo H. Bartmeier, M.D., General Motors Building, Detroit).

ASSOCIATION OF AMERICAN PHYSICIANS

A meeting of the Association of American Physicians will be held in Atlantic City on May 3 and 4 (secretary, Dr. Henry M. Thomas, Jr., 1201 North Calvert Street, Baltimore 2, Maryland).

ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

The annual meeting of the Association for the Study of Internal Secretions will be held in Boston from May 17 to 20 (secretary, H. H. Turner, M.D., 1200 North Walker Street, Oklahoma City, Oklahoma).

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, APRIL 8

THURSDAY, APRIL 8

12:00 m. Clinicopathclogical Conference. Nurses Home, Allerton Hospital, Brookline.

FRIDAY, APRIL 9

*9:00-10:00 a.m. The Problem of Local Health Units in Massachusetts. Dr. Hugh R. Leavell. Joseph H. Pratt Diagnostic Hospital.

*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

12:00 m.–1:00 p.m. Clinicopathological Conference. (Boston Floating Hospital.) Joseph H. Pratt Diagnostic Hospital.

MONDAY, APRIL 12

*12:00 m. Clinicopathological Conference. Margaret Jewett Hall, Mt. Auburn Hospital, Cambridge.

*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, APRIL 13

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY, APRIL 14

*9:00–10:00 a.m. Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon. Joseph H. Pratt Diagnostic Hospital.

*12:00 m. Grand Rounds and Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.

*2:00–3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Service. Amphitheater, Children's Hospital.

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*Open to the medical profession.

APRIL 2–30. Joseph H. Pratt Diagnostic Hospital. Medical Conference Program. Notice above.

APRIL 7. Tufts Medical Alumni Association Annual Dinner. Page 455, issue of March 25.

APRIL 7–9. American Laryngological, Rhinological and Otological Society. Page 419, issue of March 18.

APRIL 7, 9, 14 and 16. American Trudeau Society. Page 240, issue of February 12.

APRIL 8. Endometriosis. Dr. John Fallon. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

APRIL 8. Massachusetts General Hospital Research Council Meeting. Page 455, issue of March 25.

APRIL 10. American Congress of Physical Medicine. Page 344, issue of March 4.

APRIL 12. Harvard School of Public Health. Page 384, issue of March 11.

APRIL 12 and 13. American Otological Society. Notice above.

APRIL 13. Harvard Medical Society. Page 455, issue of March 25.

APRIL 13. New England Society of Anesthesiologists. Page 455, issue of March 25.

APRIL 14. New England Dermatological Society. Page 455, issue of March 25.

APRIL 15. Berkshire District Medical Society. Notice above.

APRIL 19–23. American College of Physicians. Page xiii, issue of July 31.

(*Notices concluded on page xv*)